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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Stakeholders' knowledge, attitudes and practices to pharmacovigilance and adverse drug reaction reporting in clinical trials: a mixed methods study

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Purpose

The purpose of this study was to explore the knowledge, attitudes and practices of health professionals working in clinical trials, to pharmacovigilance and adverse drug reaction (ADR) reporting.

Methods

A mixed methods study comprising an online questionnaire disseminated from September to November 2018, three semi-structured interviews and four focus groups. The qualitative components were conducted with a random sample of questionnaire participants who had provided their contact details (n = 24). The qualitative interviews were conducted at a location convenient to the participant's place of work between October and December 2018.

Results

One hundred and forty-eight participants completed the questionnaire. Study coordinators/project managers represented the largest group of participants 28.6% (n=38). Poor knowledge or understanding of ADR reporting was the most frequently cited barrier to ADR reporting, 75% (n=93). The most common enabler to reporting was having a clear understanding of an ADR definition, 85.7% (n=108). Focus group and interview participants described having limited staff as a barrier to reporting an ADR. They welcomed the prospect

of pharmacovigilance training and indicated that face-to-face training would be preferred to provision of online training.

Conclusion

This study highlights key factors that influence the reporting of ADRs in clinical trials. Although the findings are specifically related to the clinical trial environment in Ireland, they may provide a useful platform for optimising the future conduct of trials. This research suggests that ADR reporting may be improved through provision of enhanced pharmacovigilance training to clinical trial staff.

Key words

Clinical trial, pharmacovigilance, adverse drug reaction reporting.

Introduction

Pharmacovigilance is growing in importance in recent years due to the increasing number of emerging drugs and has a critical role in clinical trials, post-marketing surveillance and public health [1]. It is defined as the science and the activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [2]. The objectives of pharmacovigilance are to promote the safe and effective use of medicines by providing reliable and balanced information for the assessment of the risk-benefit profile of medicines and the minimisation of their risk [3].

The World Health Organisation (WHO) has defined an adverse drug reaction (ADR) as any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function [1]. It is widely acknowledged that ADRs constitute a major burden at the individual and societal level, both as a public health problem and an economic issue [4]. In the European Union, it is estimated that ADRs account for 5% of hospital admissions and approximately 197,000 deaths per year, resulting in a societal cost of €79 billion [5]. Pharmacovigilance is of critical importance to the field of clinical trials and plays a vital role in the assessment, monitoring and prevention of ADRs in clinical trials [6].

Randomised controlled trials are the gold standard for evaluating the efficacy of new medicines before they are released to the market [7]. However, despite the vital importance of drug safety information, evidence suggests that clinical adverse effects are adequately reported in only 39% of clinical trials [8, 9]. It is ultimately the responsibility of the clinical trial principal

investigator to ensure optimal ADR reporting in a study [10]. Inconsistency in ADR reporting has a number of significant consequences for the conduct of clinical trials and therefore has serious implications for patient safety. There are examples of patient safety issues, that were not identified during clinical trials, being highlighted in post-marketing surveillance [11, 12]. The secondary use of data from randomised controlled trials and meta-analyses can also be valuable in the assessment of drug-related harms [13, 14]. This inconsistency in ADR reporting also restricts the comparison of ADR rates across trials and it can therefore be extremely challenging to systematically review and summarise the literature on ADR reporting [15]. The consequences of these deficits vary in severity but collectively represent a challenge to effective clinical trial conduct. The dearth of research examining why ADRs are inadequately reported in clinical trials, underlines the need for a study to explore these factors. Therefore, the purpose of this study was to explore the knowledge, attitudes and practices of health professionals and researchers working in clinical trials, to pharmacovigilance and ADR reporting. Secondary objectives were to explore the reasons for underreporting of ADRs and to identify methods to optimise ADR reporting.

Methods

Study type

A convergent parallel mixed methods design was used (Figure 1). The premise of a mixed methods approach is that the use of quantitative and qualitative methods in combination provides a better understanding of research problems than either approach alone [16]. This design entails that the researcher concurrently conducts the quantitative and qualitative elements in the same phase of the research process, weighs the methods equally, analyses the two components independently, and interprets the results together [16]. In this study, the quantitative and qualitative elements were weighted equally and collected in the same phase of the research. However, it was necessary to carry out the quantitative data collection first in order to identify participants who were willing to participate in the qualitative component of the study. The purpose of the qualitative study was also to obtain a deeper and richer understanding of the responses from the online questionnaire.

The quantitative responses from an online questionnaire and qualitative responses from semi-structured interviews and focus groups were collected and analysed separately. The results of both data analyses were then integrated and synthesised during the interpretation phase.

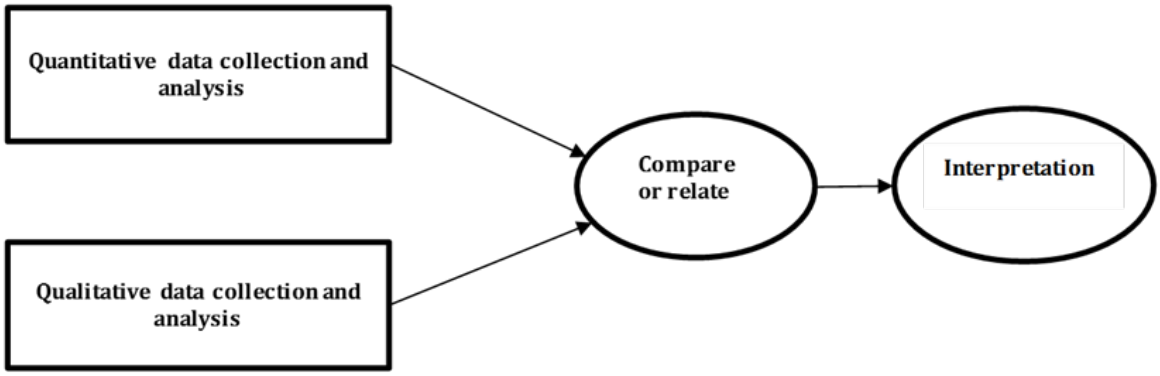


Figure 1: Convergent parallel mixed methods design

The inclusion criteria for the study were**:** healthcare professionals, researchers and others 18 years and older with experience of working in clinical trials in Ireland. The exclusion criteria for the study was**:** experience as a study participant/subject in a clinical trial.

Quantitative methods

A questionnaire for this study was developed with questions from previous studies [17, 18]. The final questionnaire was agreed by consensus of all authors. The questionnaire consisted of 24 questions in different sections that examined participant demographics such as sex, profession, qualifications, role in clinical trials, years of experience specific to clinical trials, and knowledge, practice, and attitudes towards the topic. There were a number of questions included in the questionnaire that participants could skip if they were not relevant to them.

After the first draft of the questionnaire was developed, face validity was tested using a convenience sample of five healthcare professionals and academic researchers independent of the study team. These responses were not included in the final analysis. Further iterations of the questionnaire were then developed until final agreement by all authors. A copy of the questionnaire used in this study is available as supplementary material.

The final question of the questionnaire was optional. If participants expressed an interest in attending a semi-structured interview or focus group on the research topic, they were asked to provide their contact details, that is name, job title and an email address, for follow-up contact. When the questionnaire responses were downloaded, these contact details were uncoupled from other questionnaire data and were stored separately in order to maintain the anonymity of the data. Only two members of the research team (D.O.R and J.E.) had access to the contact details.

The research team contacted the Health Research Board Clinical Research Coordination Ireland (HRB CRCI), an independent national network, providing support in the conduct of clinical trials across Ireland, to utilise their professional contacts to identify academic institutions, hospitals, professional bodies and associations, research networks and charities. The research team also assembled a list, based on their professional, academic and research networks of other organisations conducting clinical trials in Ireland.

The online questionnaire (via SurveyMonkey, https://www.surveymonkey.com/) was then emailed to healthcare professionals, researchers, data managers, trial coordinators, project managers, centre managers and study monitors working in these organisations. As it was not

appropriate or feasible to initially make direct contact with potential participants, D.O.R contacted a gatekeeper at each organisation who agreed to disseminate the questionnaire within their organisation on behalf of the study team. One reminder email was sent to all gatekeepers two weeks after initial contact. A link to the questionnaire was also posted in a Tweet on Twitter (https://twitter.com/) to capture as many participants as possible. The questionnaire was disseminated from September to November 2018.

Statistical analysis of quantitative data

Descriptive data analyses were performed using Stata® version 13 (StataCorp, College Station, TX, USA). Continuous variables were presented as mean with standard deviation (SD) and range, or median with interquartile range (IQR), as appropriate, and categorical variables as frequencies (percentage).

Qualitative methods

One month after the first questionnaire was completed, semi-structured interviews and focus groups were conducted with a random sample of those questionnaire participants who had provided their contact details. When it was not logistically possible to conduct a focus group, a one-to-one or phone interview was conducted instead.

A topic guide was developed based on the questionnaire responses, the literature, and was further developed through group discussions by all authors. It was then piloted in a focus group consisting of seven academic researchers. The pilot focus group was not included as part of the main analysis but served to test and refine the topic guide. It was also iteratively refined after

each focus group and semi-structured interview was transcribed and analysed to pursue emerging themes. Examples of the topic guide are available as supplementary material.

The semi-structured interviews and focus groups were conducted by D.O.R. at a location convenient to the participant's place of work between October and December 2018. All interviews and focus groups were audio-recorded, anonymised and transcribed verbatim by one researcher (M.K.) and checked for accuracy by another researcher (D.O.R.). They were then saved in QSR International NVivo Qualitative Data Analysis Software (V.10.22) to facilitate analysis. Field notes were written and used to facilitate preliminary familiarisation with emerging themes immediately after each interview and focus group.

Qualitative data analysis

Data were analysed using thematic analysis [19]. Two researchers, M.K. and D.O.R., independently reviewed and coded the transcripts. Initial themes were developed by M.K and D.O.R and discussed among all authors. The themes subsequently underwent further refinement in an iterative manner until all authors agreed upon the final themes.

Standardised reporting guidelines

The Good Reporting of a Mixed Methods Study (GRAMMS) framework was used to inform reporting of the findings [20]. (See supplementary material).

Ethical approval

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork University Teaching Hospitals, Cork (reference ECM 4 (pp) 05/06/18 & ECM 3 (h) 04/09/18) and from the other relevant academic institutions and hospitals in Ireland.

Quantitative Results

In total, 186 participants attempted the survey with 148 complete responses. The response rate was not calculated as this was an online survey, and therefore it could not be determined how many people received the email or viewed the Tweet.

Seventy-five per cent (n=104) of participants were female. The occupations of participants were nurses/midwives 32.4% (n=44), researchers 22.1% (n=30), pharmacists 18.4% (n=25), Consultant Physicians 5.2% (n=7), General Practitioners 2.9% (n=4), non-consultant hospital doctors 2.2% (n=3) and others 16.9% (n=23). Those who identified themselves as "others" described their clinical trials roles as data managers, pharmacovigilance officers, trial coordinators, project managers, centre managers and trial monitors.

Study coordinators/project managers represented the largest group of participants 28.6% (n=38), followed by research nurses 17.3% (n=23) and others including research pharmacists, clinical trial pharmacists, and study doctors, 17.3% (n=23) (See supplementary material). The participants mean (± SD) years of experience specific to clinical trials was 6.4 (5.9) years.

Ninety-eight per cent of participants (n=129) were familiar with the term pharmacovigilance. Almost all participants were familiar with the following terms associated with the practice of pharmacovigilance: monitoring and evaluating adverse events (94.5%, n=121), promoting safe and effective use of medicines (89.1%, n=114), benefit-risk assessment of medicines (88.3%, n=113), risk management of medicines (84.4%, n=108).

Participants were provided with a definition for an adverse drug reaction and were asked to describe their understanding of it on a scale where 1 = poor and 10 = excellent. The median (IQR) score was 8 (7,10). Approximately 72.3% (n=94) of participants reported having adequate knowledge on how to report an ADR.

Over half of participants 55.0% (n=71) were involved in the reporting of ADRs in clinical trials. For those involved in ADR reporting, 80% (n=56) identified the ADRs at participant follow-up visits, 71.4% (n=50) from participant's self-report, and 68.6% (n=48) from participant interview (in person, or by phone). The majority of those involved in ADR reporting (80%, n=56) reported the ADR to the study sponsor.

Table 1 shows the barriers and enablers/facilitators to reporting ADRs in clinical trials. The most frequently cited barriers were poor knowledge or understanding of ADR reporting 75% (n=93), lack of practical guidance about ADR reporting 59.7% (n=74) and ambiguity and inconsistency surrounding the definition of ADRs (i.e. too many definitions) 56.5% (n=70). The most common enablers/facilitators were clear understanding of ADR definition 85.7% (n=108), good knowledge of how to assess a clinical trial ADR 84.9% (n=107) and access to an online reporting portal 75.4% (n=95).

Table 1: Barriers and enablers/facilitators to reporting ADRs in clinical trials

Barriers	**% (n)**
Poor knowledge/understanding of ADR reporting	75.0 (93)
Lack of practical guidance about ADR reporting	59.7 (74)
Ambiguity and inconsistency surrounding the definition of ADRs (i.e. too many definitions)	56.5 (70)
Time restraints	44.4 (55)
Lack of agreement regarding the most appropriate strategies of ADR assessment	36.3 (45)
Lack of perceived importance of ADR reporting	36.3 (45)
Concerns about the implications of reporting the ADR to the trial regulator	26.5 (33)
Resistance/perceived resistance from other stakeholders in the clinical trial	25.0 (31)
Other	12.0 (14)
Enablers	**% (n)**
Clear understanding of ADR definition	85.7 (108)
Good knowledge of how to assess a clinical trial ADR	84.9 (107)
Online reporting portal	75.4 (95)
Perceived importance of ADR reporting by researchers	71.4 (90)
Designated reporting person (e.g. trained in the technical requirements of electronic reporting in EudraVigilance)	71.4 (90)
Availability of reporting criteria specific to ADRs	68.3 (86)
Other	4.8 (6)

Participants recognised the importance of receiving training on reporting ADRs in clinical trials and 58.7% (n=74) have attended formal workplace training (e.g. attended workshops, seminars, lectures) on this topic. The majority of participants 88.9% (n=112) reported they would avail of training in reporting ADRs in clinical trials if it was available. Participants indicated they would prefer ADR training via face-to-face workshops 62% (n=70), online courses 52.2% (n=59), webinars 30.1% (n=34), seminars 30.1% (n=34) and lectures 26.6% (n=30).

Qualitative Results

The four focus groups and three semi-structured interviews ranged from 43 min to 76 min in length (mean length 53 min). The mean duration of participant's experience in clinical trials was 11 years. The characteristics of the 24 participants that attended the focus groups and semi-structured interviews are detailed in the supplementary section.

Understanding of the terms Pharmacovigilance and Adverse Drug Reaction

All participants provided a clear and accurate description of the term pharmacovigilance. Some participants quoted the WHO definition. Others demonstrated understanding by describing the term using their own words.

"So the definition, the science and activities relating the assessment and detection of adverse reactions in clinical trials and any medicinal product."

(Participant 20, Pharmacovigilance Officer, Focus group 4)

"…The clue is in the name, it's vigilance. It's looking at the safety of a drug over its lifetime…"

(Participant 7, Quality Manager, Focus group 2)

The majority of participants correctly defined the term ADR, with some using descriptions very similar to the International Conference on Harmonisation definition.

"…it's essentially anything adverse that can happen to a patient as a result, a direct result of the pharmaceutical product in question…"

(Participant 22, Principal Investigator, Semi structured interview 1)

"A noxious or an unintended response to a drug at any dose."

(Participant 7, Quality Manager, Focus group 2)

Responsibility for reporting

Participants emphasised the importance of the principal investigator being actively involved in the conduct of the trial. Participants reported that other trial staff should not have to persuade the principal investigator to carry out their tasks. It was stressful for staff if the principal investigator was not willing to engage with them. Participants also highlighted that some principal investigators didn't place enough emphasis on their role and should prioritise this responsibility. This is particularly relevant as ADRs require immediate reporting to the study sponsor and it is the legal responsibility of the principal investigator to carry out this role.

"…if an investigator is not really hands on, then they shouldn't be doing studies. It's that important... It shouldn't be up to the nurse to be cajoling them or twisting their arm or whatever... It can be sometimes seen as not that terribly important and the investigators, if they want to do clinical trials, they need to prioritise this."

(Participant 12, Study Physician, Focus group 3)

"It's quite stressful actually, it's very stressful, I've seen coordinators, nurses getting quite stressed if a PI is too busy to engage and runs away. It's not a nice situation…"

(Participant 15, Clinical Nurse Manager, Focus group 3)

ADR reporting process

Enablers for reporting

The majority of participants indicated that the reporting of adverse events involved a paper format. Participants agreed that an electronic form would be the preferred option for reporting.

"I process the SAEs when they come in but they're still paper so I would definitely love an electronic database that sites could report……"

(Participant 17, Quality Manager, Focus group 4)

Participants described a guidance tool as being very useful when completing the reporting form. This practical guide would streamline the reporting process and reduce the risk of errors occurring.

"Some sponsors would sometimes supply a guidance tool on how to fill out the reporting form which can be really useful as well."

(Participant 16, Research Nurse, Focus group 3)

Barriers to reporting

Participants described the challenge of having a limited resource of staff, in terms of numbers of staff, experience level and the dedicated time for the staff member to report an ADR, especially when reporting suspected unexpected serious adverse reactions (SUSARs) to the relevant authorities. This was particularly stressful if a member of the team was unavailable

when a SUSAR report was due for submission. The process of collecting the relevant information and reporting the event was described as time consuming.

" ... if you get an ADR that's obviously serious and unexpected and it needs to go to EudraVigilance or the HPRA (The Health Products Regulatory Authority) and ethics that you know with those tight timelines and in that environment where you don't have a big nice PV team you're looking at a situation where you could be on annual leave and have to report a SUSAR so I would say yeah, in my environment now that's actually really challenging.

(Participant 17, Quality Manager, Focus group 4)

"I think it's important, to make sure staff have enough time to do that data capture and reporting… because there's an awful lot of time, it's not just the patient visit. It's all the reporting afterwards as well, so it is very important."

(Participant 15, Clinical Nurse Manager, Focus group 3)

Although participants acknowledged the importance of reporting adverse events, they were also aware of the possible implications associated with reporting. This could be associated with an abundance of follow-up queries for the reporter to address until the event is closed out.

" ... Like anything we report SAEs, AEs, is followed by multiple emails, multiple questionnaires, multiple follow-up letters so… we do it, we know we have to do it but it's like oh no we have to report this and you're just waiting for this wave of questions to come back to you then."

(Participant 24, Principal Investigator, Semi structured interview 3)

Relationship with stakeholders

Working with an experienced member of the trial team was described as being very beneficial. Experienced staff were a useful resource for addressing queries that their colleagues may have. This was regarded as being important as it gave staff more confidence when dealing with a principal investigator.

" ... so if you work with someone who is more experienced then you can bounce things off them and I think that's really, really important when it comes to ... things that you might not be sure of, that a more experienced research nurse would be able to help out with and then you'd have more confidence going to the PI."

(Participant 13, Study Monitor, Focus group 3)

Education and training

Some participants reported that previous pharmacovigilance training was well received by attendees and they welcomed further educational events on this topic as it was considered important.

"We did a pharmacovigilance training session some time ago and there was a very good attendance at it and people felt that it was quite helpful, so I think we probably need to do more of them…."

(Participant 12, Study Physician, Focus group 3)

Participants suggested face-to-face training would be more beneficial compared to an online version, as the latter format of training could sometimes be time restrictive. Face-to-face training enhanced the learning experience as it provided an opportunity to interact and discuss pharmacovigilance related matters with the facilitator and fellow attendees.

"You see I find face-to-face works really well but I know there's a big push for blended learning and webinars, a webinar could work but then you tend to have to keep them very time limited because it tends to be pushed into three quarters of an hour or something like that…"

(Participant 18, Clinical Nurse Manager, Focus group 4)

"And you can ask questions then or give specific examples of you know instances you've come across in pharmacovigilance and just get another opinion, you can't do that online really."

(Participant 13, Study Monitor, Focus group 3)

Participants suggested that an accredited course such as Good Clinical Practice (GCP) training was very beneficial especially for principal investigators and sub-investigators as it provided a platform for outlining their roles and responsibilities within a trial.

"I think having foundation knowledge in relation to having GCP training, an accredited course is very important so that the investigator and sub-investigators know their responsibilities and therefore they will always have a reference text in knowing their responsibilities."

(Participant 23, Principal Investigator, Semi structured interview 2)

Discussion

This study used a mixed methods approach to explore the factors that influence the reporting of ADRs in clinical trials. Participants reported having a good knowledge and understanding of pharmacovigilance and ADRs. Key enablers to ADR reporting were having a clear understanding of an ADR definition, knowledge of how to assess a clinical trial ADR, having access to an online reporting portal and the perceived importance of ADR reporting by researchers. Key barriers to ADR reporting were having poor knowledge of ADR reporting, lack of practical guidance, time restraints, lack of perceived importance, resistance from other stakeholders in the trial, implications of reporting and having limited staff resources. Pharmacovigilance training was valued by the participants.

It is imperative that all stakeholders involved in clinical trials have a comprehensive understanding of the key concepts associated with pharmacovigilance and drug safety. This can optimise the key aspects of preventing, recognising, managing and reporting of ADRs. In non-clinical trial settings, it has been reported that fewer than half of participants were familiar with these concepts [21, 22]. It is evident from the findings of the present study that the population was very knowledgeable about clinical trials and had a clear understanding of the term's pharmacovigilance and ADR. This is very reassuring given the importance of these concepts in the clinical trial field and perhaps not unexpected given the experience of the study participants.

Training and education on ADR reporting in clinical trials was emphasised by participants. Findings from the literature suggest that educating investigators, sponsors and others involved in clinical trials on the best practices with regards to relating an adverse event to a medicinal product can optimise the consistency of the reporting process [23]. Although fifty-per cent of participants in the questionnaire indicated that online courses would be their preferred type of training, those who were interviewed indicated a preference for face-to-face training over the provision of online training. Wutoh *et al.* carried out a review of internet-based continuing medical education. The study demonstrated that this method of education delivery is just as effective at generating knowledge compared to traditional formats. However, there is little evidence to suggest the positive changes in knowledge are translated into changes to practice [24]. A future study could compare the impact of face-to-face training to an online course with regards to ADR reporting.

Interestingly, interview participants identified that Good Clinical Practice (GCP) training is very important for investigators throughout their career. It is imperative that all personnel involved in regulated clinical trials are trained on international standards such as GCP [10]. Although pharmacovigilance and ADR reporting are included in GCP training, clinical trial staff expressed a desire for additional pharmacovigilance training.

A key finding from the interviews indicated that working with an experienced member of the trial team was beneficial. George *et al.* highlighted that the quality and experience of a clinical research team are considered important components to the success of adverse event reporting, particularly in early-phase cancer trials [23]. This should be a key consideration for clinical

trialists when establishing a trial team. In addition to pharmacovigilance training, a formal mentorship programme for early-career researchers may be beneficial during the set-up of the clinical trial.

The potential role of an online reporting portal was emphasised in this study with participants suggesting it would optimise the reporting of ADRs in clinical trials. It is documented that traditional resources used for ADR reporting such as paper forms can lead to inaccuracies in data collection and inefficiencies in the reporting process [25]. The use of clinical trial electronic portals has gained popularity in recent years. Electronic portals offer the opportunity to reduce time and costs associated with paper-based reports. They also provide the benefit of a security measure with document management through the use of password protected log-in [26]. Given the strong preference for this method of reporting and with evidence supported from the literature, online ADR reporting should be recommended in all future trials. It is likely that more efficient and better reporting will result, and this may lead to the overall improvement in patient outcomes.

The lack of practical guidance was reported as the most common barrier to ADR reporting among those who completed the questionnaire. Responses from the interviews indicated that a guidance document would be very beneficial for staff when completing the reporting form. This attests to the need for the sponsor to engage with the PI during the development of the study protocol to ensure that the most relevant and practical resources are used to streamline the reporting process.

Time restraints and limited staff numbers were highlighted as a key barrier to ADR reporting in this study. George *et al.* support this finding and described the time-consuming process for an investigator to gather sufficient data for review and determine the relationship between the adverse event and study treatment [23]. The qualitative findings reported the challenge of having limited staff to report an ADR. Mirbaha *et al*. highlighted that a lack of human resources was one of the factors that hampered the reporting of adverse drug events [27].

A lack of perceived importance of ADR reporting and resistance from other stakeholders in the trial were considered as barriers to reporting. Participants reported their frustration and cited the challenge of working with principal investigators who fail to bear responsibility for their role. In many cases, principal investigators have busy clinical schedules, and for some, this may infringe on time to carry out their research role. It is important that investigators successfully meet all research expectations when conducting a clinical trial. They should be aware of all events especially serious or unexpected events as these need expedited reporting to the relevant authorities. [28]. According to the principles of the International Conference on Harmonisation GCP one of the key responsibilities of the PI is to ensure that the site reports an adverse event immediately to the study sponsor on becoming aware of it [29]. One solution may be to delegate certain responsibilities and tasks to sub-investigators. The sub-investigator can deputise for the PI for phone calls, laboratory result reviews, adverse event assessments, informed consent, and be prepared to answer questions on behalf of the PI if they are unavailable [30] .

Concerns regarding the implications of reporting the ADR to the trial regulator was also considered a barrier. Participants who were interviewed indicated their concerns regarding the possible implications associated with reporting such as addressing multiple follow-up queries. Responding to queries can be time consuming and become a burden especially for clinical trial sites that are under resourced with staff. This can contribute to an under-reporting of adverse events and therefore lead to a false perception of the benefit-risk ratio of drugs which can affect many stakeholders including patients, clinicians, drug developers and regulators [31, 32]. Further work should be carried out to identify the most efficient ways to streamline the follow-up query process. It is essential to obtain the views from all the relevant stakeholders in this process including principal investigators, representatives from study sponsors and competent authorities in order to design a fit-for-purpose electronic system that maintains the integrity and detail required of a clinical trial reporting system while meeting the needs of clinical trial personnel.

Implications for policy and practice

The findings from this study are important for researchers conducting future clinical trials as it highlights barriers and enablers to ADR reporting. The findings also suggest that additional training and support are required for effective ADR reporting and monitoring. Academic institutions should consider incorporating content on pharmacovigilance and ADR reporting into the curriculum for undergraduate healthcare programmes, especially in pharmacy, nursing and medicine. The WHO pharmacovigilance core curriculum for university teaching have formulated competencies and key clinical aspects that can be integrated into existing courses

such as pharmacology and pharmacotherapy or used as a stand-alone course [33]. The WHO International Society of Pharmacovigilance have created a comprehensive, detailed and balanced curriculum for pharmacovigilance education [34]. Rosebraugh *et al.* developed an ADR quality reporting education intervention program presented to 4th year medical students on a clinical pharmacology rotation. The study demonstrated that the 15-minute intervention significantly improved the overall quality of ADR reporting [35]. Educating students at university level may improve their knowledge about the safety of medicines and equip them with the relevant skills for the safer use of medicines throughout their career [36, 37].

Strengths and limitations

This is the first national study on pharmacovigilance and ADR reporting in clinical trials in Ireland. The use of a mixed methods approach which combined quantitative and qualitative data facilitated a richer analysis. The qualitative interviews were arranged with participants over a three-month period and this facilitated prolonged engagement with the data. The generalisability of the study findings may be limited by the inability to calculate a response rate. However, the broad inclusion criteria and background of participants with an extensive representation of clinical trial expertise help ensure that the findings reflect the most important factors that influence the reporting of ADRs in clinical trials in Ireland.

While 75% of participants were female, this may simply reflect the gender balance within the clinical trial environment in Ireland. The focus groups were organised at locations and at times to maximise participation, however despite these efforts, no PI was available to attend due to their workload and time pressures. Therefore, the qualitative interviews were only conducted

with PIs. The qualitative data collection was conducted by one researcher (D.O.R), however dependability was enhanced by using a multidisciplinary team input: pharmacists (D.O.R., M.K., K.A.W., M.B.), epidemiologist (F.S.) and physician (J.E.) during data analysis (investigator triangulation).

Conclusion

This study highlights key factors that influence the reporting of ADRs in clinical trials. It is imperative that all stakeholders involved in clinical trials have a comprehensive understanding of the key terms associated with ADR reporting. Enhanced pharmacovigilance training should be recommended to all clinical trial staff as this may improve ADR reporting. Online reporting offers a more efficient way of optimising the reporting process. Principal investigators should consider delegating responsibility to sub-principal investigators and other members of the team where necessary.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by David O Riordan, Mary Kinane, Kieran A. Walsh, Frances Shiely, Joe Eustace and Margaret Bermingham. The first draft of the manuscript was written by David O Riordan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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