



Strengthening Clinical Trial Pharmacovigilance: Simple Interventions Improve Communication Over Serious Adverse Events

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ABSTRACT

With over 100 drugs in the development pipeline, this is an exciting time for drug development in Cystic Fibrosis (CF). However, the increased number of trial participants brings challenges. Unscheduled admissions of clinical trial participants are defined as Serious Adverse Events (SAEs). Good Clinical Practice (GCP) guidelines mandate prompt reporting of SAEs to optimise pharmacovigilance and protect patient safety. As our trial cohort grew, so did our trial team, with junior roles becoming trial or clinical specific. Consequently, we encountered delayed awareness by the trials team of unplanned admissions. We conducted a quality improvement (QI) project to empower clinical teams to act as a safety net to alert trial teams to admissions of trials patients to improve patient safety and optimise pharmacovigilance through timely SAE reporting on clinical trials.

We show that simple interventions can substantially increase the percentage of clinical staff who routinely ask about trial participation at admission, the percentage of staff who would inform the trial team of an admission if they identified that a patient is on a trial, and the percentage of clinical staff who know how to contact the trials team. This significantly reduced the number of days until trial teams became aware of admissions of trial patients from a median (range) of 18(2-93) days to 1(1-3) days ($p < 0.0001$). This is likely to benefit patient safety through ensuring SAE reporting requirements are met.

Our findings have relevance to improving pharmacovigilance through timely SAE reporting across many disciplines conducting clinical research with chronic disease cohorts. With increasing recognition of the need to improve standards of care for research patients, we encourage other research-active teams to implement such interventions to improve patient safety. We especially suggest increasing trial activity visibility to clinical teams, who recognised how their engagement in research can benefit patient safety and their own professional development.

Keywords: Pharmacovigilance; Cystic fibrosis; Standard practice; Patient safety

INTRODUCTION

Key points

Good Clinical Practice mandates prompt reporting of SAEs to optimise pharmacovigilance and improve patient safety.

Delays in reporting of SAEs can arise, particularly when teams are large, divided into predominantly clinical or predominantly trials roles, or based in physically different environments.

Here we show that a few simple interventions can empower clinical teams to act as a robust safety net to ensure the trial team became aware of unplanned admissions.

Many of our interventions are transferable to all teams conducting clinical trials with cohorts of patients with chronic

diseases to improve patient safety on clinical trials and optimise pharmacovigilance through prompt SAE reporting.

We would particularly encourage increasing visibility of trial activity so clinical teams understand how their engagement in research can benefit patient safety, service delivery and their own professional development.

Background

This is an exciting time for drug development in many chronic diseases including cystic fibrosis (CF) [1-3]. With over 100 drugs in the CF trial pipeline, the number of trials conducted each year is increasing rapidly and a greater proportion of the clinic population is participating in trials [1,4,5]. Improving standards of care for patients taking part in trials has lagged behind the clinical space.

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However, in recent years, there has been a welcome shift in this paradigm, with organisations such as The National Institute for Health Research and the Royal College of Physicians placing increased emphasis on improving patient experience and safety when taking part in trials [3].

Unscheduled admissions during a clinical trial are defined as Serious Adverse Events (SAEs). To ensure adequate pharmacovigilance, Good Clinical Practice (GCP) guidelines [2] mandate prompt reporting of these SAEs. Additionally, timely awareness on the part of the trial team means they can implement any required protocol procedures and assist clinical teams with aspects of trial care such as drug interactions. Many chronic diseases, including CF, can be characterised by periods of relative stability punctuated by exacerbations leading to hospital admission. These admissions must be promptly recognised and acted upon, and as such it is vital that robust systems are in place to ensure trial teams identify when trial patients with chronic diseases are admitted to hospital.

Local problem

The CF trials team at our centre has grown rapidly over recent years and now recruits one of the highest numbers of adult and paediatric CF patients into drug trials in Europe [6]. Despite senior team members being both clinically and research active, more junior members were appointed to research-specific roles within the adult and paediatric space. This separation from the clinical team and the increased numbers of recruits led to problems with delayed trial team awareness of unscheduled admissions. At consent, and during subsequent appointments, trial participants are asked to inform their research team of unplanned hospitalisations. Patients are given contact details of their study coordinator and usually at least one of the investigators. However, perhaps secondary to the stress of the admission, patients at our site tended to forget. This was particularly the case in long-term open label trials, where boundaries between clinical and trial care can become blurred in patients' minds [7], but GCP requirements remain as rigorous. Patients reported an assumption that the clinical team was automatically flagging admissions on their behalf or that trials teams would always be aware of all ward admissions. This poses a challenge when research and clinical teams have clearly demarcated roles, are not in close, frequent communication, when there are multiple wards and departments involved or when teams are based in physically separate environments.

Solution

We recognised that the clinical teams could be empowered to act as a robust safety net to ensure the trial team became aware of unplanned admissions. This would improve patient safety, make trial care easier for clinical teams, optimise pharmacovigilance and maintain GCP.

Aims

To educate the clinical teams of the importance of identifying that a patient is on a clinical trial and flagging their admission to the trial team.

To make it as simple as possible for the clinical team to identify that a patient is on a trial and get in touch with the trial team.

MATERIALS AND METHODS

Quality Improvement (QI) cycles

We conducted a 3 cycle Quality Improvement project. Specific

ethical approval for this QI project was not required. We prospectively registered the project with our centre's QI department.

Cycle 1: We designed a short questionnaire to assess whether clinical teams routinely ask about trial participation, are aware of why this is important and gauge how easy they find it to contact the trials team (Table 1). We disseminated the questionnaires to doctors, nurses and Allied Health Professionals (AHPs) at teaching and handover sessions during the first two weeks of February 2018. In parallel, we audited admissions of trials patients and recorded the length of time between admission and the trials team becoming aware of the admission. To ensure that any proposed interventions were beneficial to busy clinical teams, we asked them to suggest relevant interventions in a free text section of the questionnaire. We met with the Multi-Disciplinary Team (MDT) to develop interventions, which we implemented in late February 2018 as follows:

Table 1: Percentage of staff demonstrating awareness of procedures at baseline and after Cycle 1 interventions.

	Baseline February 2018 (n=25) 8 doctors 10 nurses 7 AHPS	Post cycle 1 interventions August 2018 (n=32) 11 doctors 10 nurses 11 AHPs	p (Fisher's exact)
Number (%) of staff who routinely ask about trial participation at admission	2 (8%)	6 (19%)	0.44
Number (%) of staff who would inform the trial team of an admission if they identified that a patient is on a trial	4(16%)	20 (63%)	<0.001
Number (%) of staff who know how to get in touch with the trials team	5 (20%)	21 (66%)	<0.001

Trials team gave a series of talks to the MDT at handover, teaching and induction sessions explaining why this issue was important and providing the roadmap for communication

The trials team added names of trials patients and trial team contacts to the adult and paediatric doctors' handover/admissions list and this is updated approximately monthly

Requested trial participation to be noted in all clinical correspondence e.g. discharge summaries and clinic letters. Once this had been added to the problem list, it tended to be carried forward into the next clinical correspondence

The trials team continued to highlight the importance to patients of informing the trial team of admissions at each contact, and reissued patients with a wallet-sized contact card

We redistributed the anonymous questionnaires six months after interventions were implemented.

Post-intervention, there were significant improvements in the proportions of staff demonstrating awareness of procedures (Table 1). Furthermore, in the 12 months pre-February 2018 there had been a median (range) of 18 (2-93) days before the trials team

were made aware of 8 admissions. In the 12 months following interventions, this was 2 (1-4) days (5 admissions) ($p < 0.0001$, Fisher's exact).

Cycle 2: Despite significant improvements in 2 of 3 questions, the number of staff proactively asking about trial participation when admitting remained low and trial participation was not always noted in annual review/clinic letters. Therefore, we supplemented our initial interventions.

A prompt was added to the annual review proforma and to the admission booklet to ask about trial participation

The trials team piloted a trial visit communication template with instructions about what to do if patients get admitted whilst on a trial and trial team contact details. This letter was uploaded onto the patient's electronic record after each trial encounter. This was later incorporated into the trials teams' standard practice.

We redistributed the questionnaire a 3rd time in August 2019, 18 months after the start of our project (Table 2).

Table 2: Percentage of staff demonstrating awareness of procedures at baseline and after cycle 2 interventions.

	Baseline February 2018 (n=25)	Post cycle 2 interventions August 2019 (n=29)	p (Fisher's exact)
	8 doctors	10 doctors	
	10 nurses	9 nurses	
	7 AHPS	9 AHPs	
		1 unknown	
Number (%) of staff who routinely ask about trial participation at admission	2 (8%)	15 (52%)	<0.01
Number (%) of staff who would inform the trial team of an admission if they identified that a patient is on a trial	4(16%)	20 (69%)	<0.001
Number (%) of staff who know how to get in touch with the trials team	5 (20%)	20 (69%)	<0.001

We received 29 responses which showed that the improvement in the number of staff who knew to inform the trial team of admissions and how to contact the trials team had been sustained, or indeed slightly improved between Cycle 1 and Cycle 2. The number of staff proactively asking about trial participation rose from a baseline of 8% to 52% ($p < 0.01$) reflecting substantial change in practice but highlighting the need for continued work. Audit of admissions data showed the improvement in time to trial team awareness of admissions was sustained between February 2019-2020 at 1 (1-3) day (6 admissions).

Cycle 3: The initial sets of interventions made important inroads. However, the percentage of staff proactively asking about trial participation remains inadequate. Therefore, we are introducing a third round of interventions

We will add a sticker to drugs prescribed through trials pharmacy reminding patients and clinicians to inform the trial team of admissions and how to contact the team; this should be seen by

the admitting clinician when writing the drug chart

We are engaging with IT services to add a flag to the e-prescribing system and electronic patient record.

We will continue to monitor admission data and repeat the questionnaires at annual intervals to ensure change is sustained and identify areas requiring further improvement.

RESULTS AND DISCUSSION

Strengths and limitations

We have initiated cycles of "Plan, Do, Study, Act" (PDSA) assessment to identify and implement appropriate and sustainable changes. The use of a nationally approved QI model is a key strength of this project [8]. Additionally, this complex issue required a multifaceted approach and continuous assessment cycles in order to ensure that the changes were relevant, sustainable and had maximum impact. We were able to implement multiple cycles and develop a sustainable plan for continuous reassessment moving forward.

We understand that the clinical teams can be extremely busy and as such had some initial concerns that this project may feel as though it is adding to their work load, particularly for more junior team members who may have had very little exposure to clinical research and may not always perceive its relevance to their day to day practice. One of the critical features of this project was close collaboration between trial and clinical teams to ensure interventions were not perceived as unduly arduous and to help the clinical team understand how these issues would help them to deliver optimal patient care. We were aware from the outset that this project may require a culture shift in order to ensure maximum impact and relevance and this can be virtually impossible to measure objectively. However, by using direct questioning and audit data we demonstrate areas of objective change. Encouragingly, many people from both sides have informally fed back that they sense a shift in the way that trial and clinical care have become better integrated at our site.

One of the limitations of this study is the use of self-reporting through questionnaires, which may lead to staff giving a public account of what they perceive to be the 'right' answer, rather than reporting their actual routine practices. However, the first round of the questionnaire suggests that this was not the case, with very small percentages of staff selecting what might be generally perceived to be the 'right' answer. The anonymity of responses may have mitigated for this potential source of bias.

However, the anonymity introduced another challenge to the analysis as we are not able to tell how many respondents answered in 1, 2 or 3 rounds. As such, it is hard to draw full conclusions as to whether the changes have fully penetrated the department or reached out to a particularly engaged group of respondents. The audit data from admissions does support that whether the changes reached the whole department or an engaged subset of clinical staff, the interventions were able to result in objective, tangible improvements in outcomes i.e. a significant reduction in length of time between admission and awareness by the clinical team of the admission [9,10].

CONCLUSION

Developing a safety net to ensure that the trial team became aware of admissions necessitated a multifaceted approach and continuous

reassessment cycles. However, we have shown that a few low cost, simple interventions can significantly reduce the number of days until trial teams become aware of admissions of trial patients. This improves patient safety, optimises pharmacovigilance, and ensures GCP reporting requirements are met. Differences in clinical and trial care delivery, size and structure of teams, physical location of teams and IT systems need to be considered. However, we suggest many of our principles are relevant to other specialities conducting clinical trials with chronic disease cohorts and to other areas of communication about trials patients. Given the recent shift in focus to improving patient safety and experience of patients on clinical trials, we would encourage centres to identify and implement such interventions.

Clinical teams can be extremely busy, and we had concerns this project may be perceived as adding to workload, particularly for team members with little previous research exposure who may not appreciate its relevance to their practice. We were encouraged by the enthusiasm with which this QI project was received. Clinical teams recognised how it can improve patient safety and how it can provide them with easier access to support. We were asked by medical, nursing, physiotherapy and play specialist teams to give sessions about CF research and active trials to support their learning and care delivery. Several people have informally fed back that they sense a culture shift which we feel will be crucial in sustaining the changes. We would particularly encourage increasing visibility of trial activity so clinical teams understand how their engagement in research can benefit patient safety, service delivery and their own professional development. This is likely to foster a positive research culture, which has been shown to improve patients' research experience and enhance learning opportunities for clinical staff.

CONFLICT OF INTEREST

RD, KH, JM and SS have no conflicts to declare. JCD has served on advisory boards and participated in clinical trial leadership, educational activities and grant review board activities for a number of pharma companies active in CF clinical trials: Vertex, PTL, Galapagos, AbbVie, AlgiPharma, Chiesi, Enterprise, Teva, Ionis,

Eloxx, Roche, Gilead. NJS has participated in advisory boards for Vertex, Chiesi, Pulmocide and Roche. He has received payments for speaking engagements from Vertex, Gilead, Chiesi, Teva and Zambon.

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