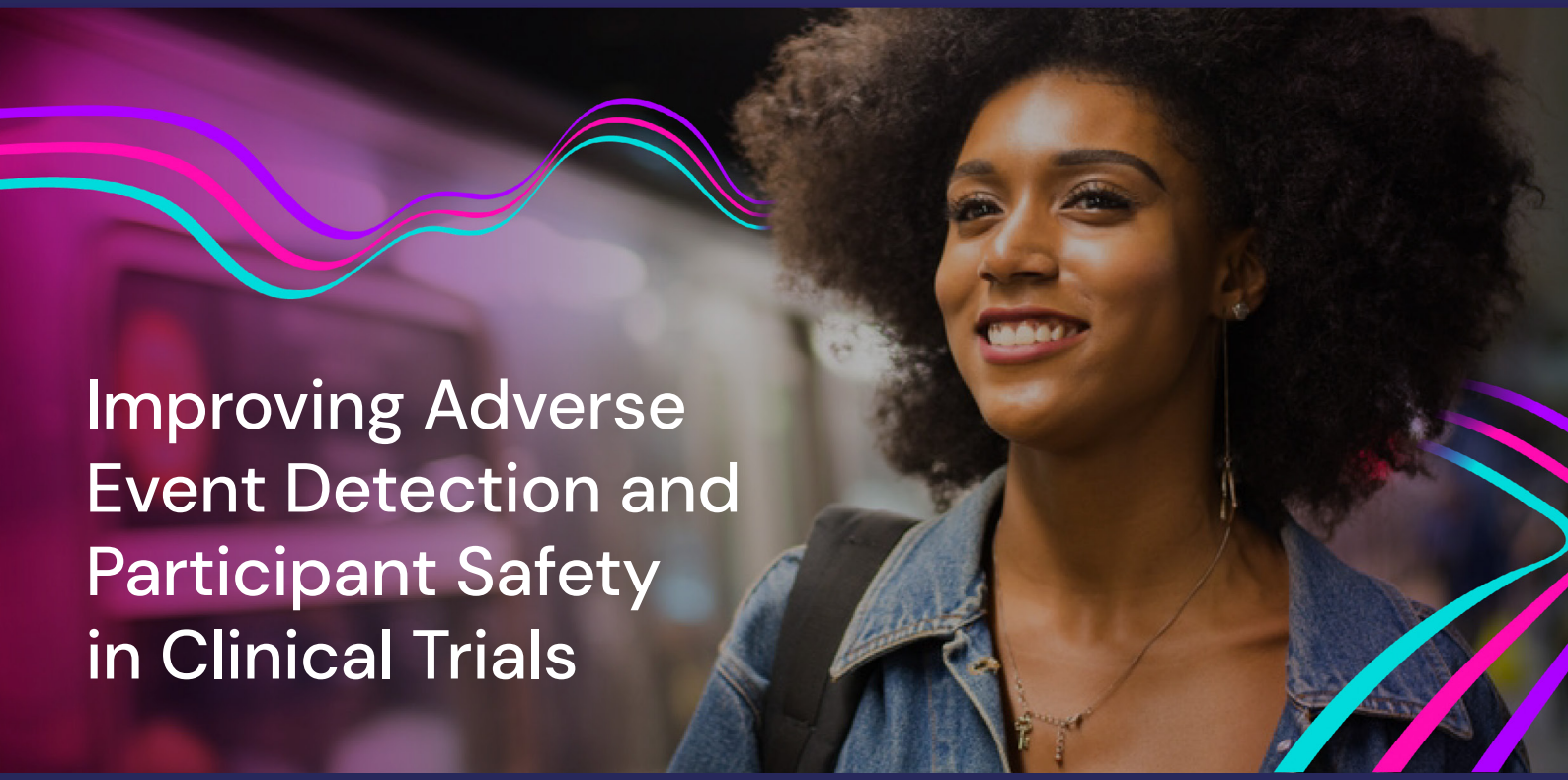
White Paper

NWEH



Improving Adverse Event Detection and Participant Safety in Clinical Trials

Introduction

Clinical trials are crucial for new drugs or interventions to gain regulatory approval, with early and accurate detection of Adverse Events (AEs) being a key priority. However, they generally focus on efficacy and common side effects, often missing rare or long-latency events. Data quality is further compromised by underreporting, recall bias, and the Hawthorne effect*. In addition to this, selective trial populations often exclude patients with complex comorbidities, those on multiple medications, or those individuals at extremes of age. As a result, the true risk-benefit profile of a drug remains incomplete at the time of market approval. Enhancing safety monitoring through real-world evidence (RWE) and innovative technology enables early detection of AEs, directly improving patient safety and inform robust regulatory decision-making.

*The Hawthorne effect refers to a change in an individual's behaviour in response to being observed, which can influence the outcomes of studies or interventions.

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Current Challenges in Safety Reporting

Advances in data collection techniques are incredibly well developed. However, this progress has not been matched for safety reporting. The process of identifying and reporting AEs is still fraught with human error and inefficiency and is extremely time and resource intensive. AE reports are the most critical way to monitor participant safety during a clinical trial, however this method is largely passive and relies almost entirely on information collected by the investigators and the research team. The accuracy of this process is therefore dependent on the quality and consistency of reporting during the trial.

the most fundamental constraint to safety data collection is the reliance on patient re-call

Underreporting by investigators is well recognised (van Hunsel F, 2012)) often due to competing responsibilities that take priority over research activities. Reporter bias can also be a limiting factor, investigators may unintentionally deprioritise safety reporting during a clinical trial in context of their wider workload.

Another challenge is the potential for the Hawthorne effect, where participants are acutely aware of their involvement in the trial due to frequent study visits and interaction with the research team, which can alter how they report their symptoms, leading to biased safety data (McCambridge J, 2014 Mar). Perhaps the most fundamental constraint to safety data collection is the reliance on patient re-call. This method has clear limitations, because participants may struggle to remember safety events or recall specific symptoms, particularly if they occurred some time ago, or the participant was too unwell to report them at the time.

Causality assessment can also present further challenges as investigators may attribute AEs to underlying conditions rather than the investigational drug. Furthermore, inconsistencies in the classification of AEs across trial sites can create variability, ultimately affecting data quality and the overall safety profile of a drug.

Implications for Patient Safety

The implications of inaccurate or missing safety data in clinical trials are profound. Clinical trials serve as the foundation for gathering critical safety information, which regulators rely on to determine whether to approve a drug or intervention.

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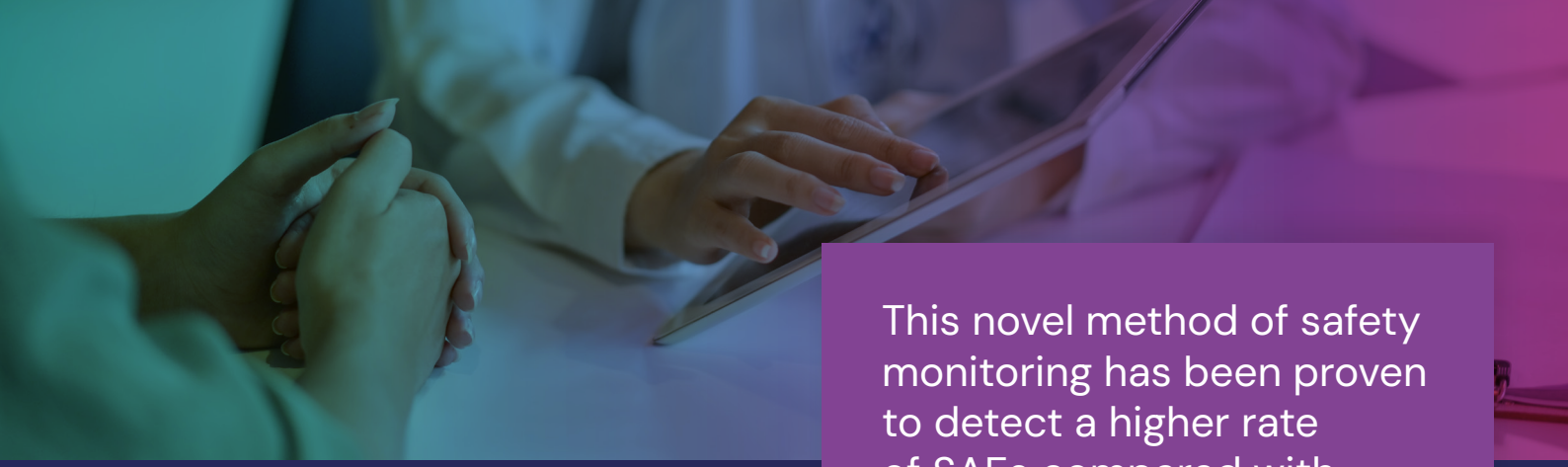
Without comprehensive and accurate safety data the true risk benefit of a drug or intervention is unknown at the point of market approval. AEs that were not detected during the trial phase will potentially go undetected once the drug reaches the market. This is largely due to the passive nature of post-marketing surveillance, which relies heavily on healthcare professionals and patients to voluntarily report AEs back to the sponsor or regulatory body such as the Medicines Health Regulatory Authority (MHRA). As a result, even after approval there are significant gaps in the understanding of the safety profile for a drug or intervention. Patients are unlikely to be aware of this and often have a false sense of reassurance, assuming regulatory approval equates to a complete understanding of a drug's risks. This may cause side effects to be underreported which could further compound the challenge of gaining a true post-marketing safety profile.



This novel method of safety monitoring has been proven to detect a higher rate of SAEs compared with traditional methods

Innovative Solutions of using Real World Evidence

RWE studies are increasingly being developed to assess the effectiveness of new drug therapies. For clinical trials to be of value they have to reflect a broader, more representative population over a longer timeframe, and provide information on comparators and outcomes that are not normally part of a traditional clinical trial protocol.

Innovative data collection methods were employed in a recent clinical trial, with key study endpoints collected directly from participants' electronic health records (EHRs). The trial was purposefully designed with broad inclusion criteria to better reflect the real-world populations likely to receive the treatment after approval. To preserve external validity, participant contact was kept to a minimum by the research team, to avoid interference with their normal routines. Safety endpoints for the study included Serious Adverse Events (SAEs) and AEs, leading to treatment discontinuation.

The utilisation of NWEH's ConneXon platform for remote safety monitoring, allowed for real time surveillance of participants, whereby medical events captured in the participants' EHR automatically triggered alerts to the research team, which prompted an immediate clinical review of the event. The alerts have been developed largely based on the standard regulatory definition of a SAE e.g., a hospital admission. Additional alerts also include medical events which have historically been associated with adverse drug reactions and are therefore worthy of heightened vigilance, examples of these alerts include liver damage, neutropenia, and acute renal failure. Safety alerts were then reviewed by the research team, along with any available additional information to determine whether they met the protocol defined criteria for an SAE. This novel method of safety monitoring has been proven to detect a higher rate of SAEs compared with traditional methods for collecting safety information (Collier S H. C., 2017).

To assess the accuracy of ConneXon, trial metrics were collected on the method of SAE detection. Noticeably, **83% of SAEs** were identified through the ConneXon data platform. Participant's themselves reported just **4% of SAEs**, despite being provided with an emergency card instructing them to do so.

However, no SAEs were reported by the study investigator, despite Good Clinical Practice (GCP) requirements for investigators to report SAEs for their patients.

17% of SAEs were not detected by the ConneXon platform. Review of these cases highlighted several contributing factors, including events occurring outside the study's data capture window or after participant withdrawal, making them absent from routine feeds. Some were reported informally via phone calls or verbal recall and not entered into the EMR, making them undetectable by ConneXon. Others were identified through NHS Digital reconciliation, highlighting integration delays.

In response to these findings, we are improving how data is captured and classified to enhance the platform's ability to detect safety events and strengthen overall monitoring using real-world evidence.

Breakdown of SAE Detection Methods

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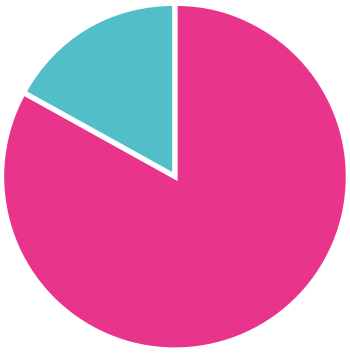
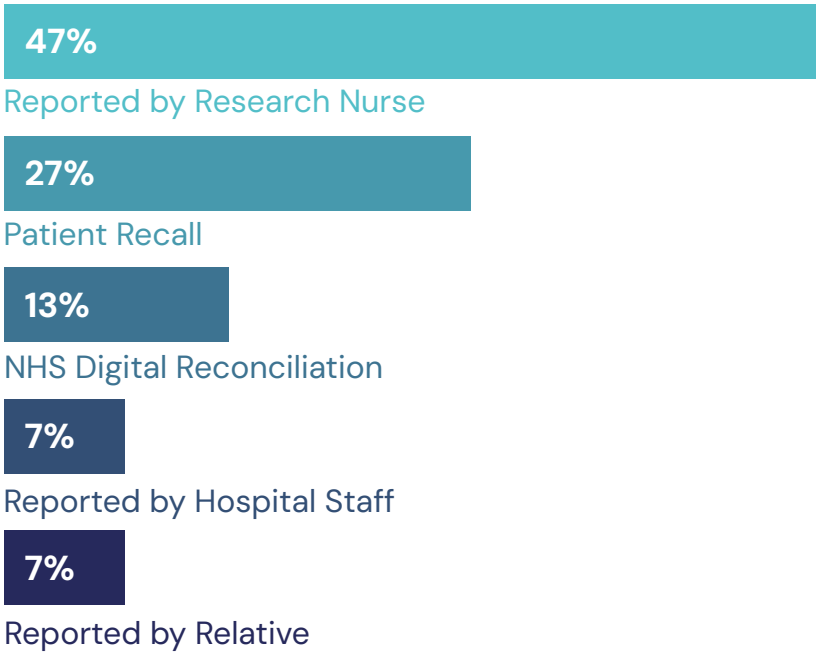
SAE Detected by ConneXon



83% SAE detected by ConneXon

17% SAE not detected by ConneXon

SAEs not detected by ConneXon %



Delayed Reporting of SAEs not detected by ConneXon

In instances where SAEs were not captured through automated monitoring, subsequent case reviews revealed substantial delays in reporting, ranging from several months to nearly a year. These included serious conditions such as chest pain, tumour diagnoses, and infections, which were identified only through retrospective data reconciliation rather than proactive safety oversight. This delay underscores the limitations of relying solely on investigator or participant-initiated reports.

Implications for Patient Safety and Trial Design

The use of real-world data sources for monitoring safety has a key advantage over traditional methods of AE capture, in that the integration of multiple healthcare data sources allows for more comprehensive and accurate data to be collected, and the ability to monitor participants' more closely, in real-time. This early detection of safety events allows the research team to intervene much sooner, reducing the risk of injury to participants. In contrast, traditional safety reporting procedures can take weeks or even months to identify SAEs or be entirely missed through underreporting.

This approach to AE detection not only provides sponsors with better quality safety data for their products but reduces the resource burden on the investigators and research teams. In addition, it enables safety concerns to be detected much more quickly than in a traditional clinical trial, ensuring a more accurate assessment of a treatment's true benefit-risk balance.

Conclusions and Recommendations

This study highlights a critical gap in the detection of SAEs in clinical trials. ConneXon successfully detected 83% of SAEs, demonstrating its effectiveness in real-time adverse event monitoring.

Traditional safety reporting remains heavily reliant on investigators and participant re-call. It could be estimated that more than half of SAEs may go undetected without the support of real-time digital monitoring (Collier S H. C., 2017). Furthermore, for those SAEs that were eventually reported through traditional methods, our findings show reporting was often significantly delayed, sometimes by several months, adding additional risks to participant safety and the ability to act quickly on emerging safety concerns.

By embedding technologies like ConneXon into clinical trials, we can significantly improve the completeness and timeliness of safety reporting. This approach reduces the burden on investigators, enables earlier identification of safety events, and ultimately strengthens participant protection and regulatory decision-making through more accurate, real-world safety data.

To address these challenges, we recommend:

- Adapting real-time monitoring into trial design to optimise the efficiency and accuracy of collecting safety data.
- Encouraging sponsorship, regulatory and researcher interaction to help advance the implementation of new methods for safety monitoring.
- Investment in safer reporting technology to ensure the collection of more representative and reliable safety information from clinical trials.

By taking these steps, clinical trials can provide a more accurate representation of drug safety, so that regulatory decisions and patient care are based on the most complete data possible.

How does ConneXon improve safety reporting in clinical trials?

ConneXon is a secure, validated Electronic Data Capture (EDC) system that transforms the way clinical trials are conducted. Built by NWEH to accelerate trial timelines while enhancing participant safety, ConneXon enables fully decentralised trials allowing individuals to participate via their local GP or from their own homes.

ConneXon's active surveillance technology allows the collection of real-world data directly from the source, offering close to real-time safety monitoring by alerting the research team with 24 hours of an event being recorded in the participants EHR.

Researchers are able to broaden study protocols, to include participants that may have previously been excluded, with the confidence that they can react quickly to any adverse reactions. The reduction of data validation overheads and accelerating endpoint identification ensures ConneXon cuts trial costs significantly and ensures rapid provision of study data.

Advanced SAE reporting

As part of ConneXon's growing capabilities, in June 2024, NWEH was proud to announce the launch of the new SAE reporting functionality, SAEfe. SAEfe is a revolutionary advancement, promising to save up to 70% of the overall costs associated with reporting adverse events, while simultaneously enhancing patient safety..

SAEfe seamlessly automates SAE reports with data directly from the EHR record, additional conditions and pertinent information can also be easily added to the SAE report, adhering to ICH GCP standards. Once the report is saved it is electronically submitted as an Individual Case Safety Report (ICSR) straight to the sponsor's study database, allowing for faster and more accurate data collection while maintaining the highest standards of safety and compliance.

As NWEH continues to advance its technology, the SAEfe system emerges as a pioneering solution to the underreporting of adverse events. By leveraging data and embracing innovative technologies, SAEfe enhances outcomes for both participants and healthcare providers.

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