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# Advancing Patient Safety Through Inclusive Clinical Trials: Harnessing Real-World Data Directly from Source

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# Introduction

This white paper focuses on the critical issue of inclusivity and diversity in clinical trials. We propose innovative solutions to bridge the gap between research and real-world healthcare with particular emphasis on the importance of these factors in improving patient safety and healthcare outcomes. Regulatory bodies will also be featured as playing a pivotal role in promoting inclusivity and diversity through the development of new guidance and legislation. Our objective is to leverage technology and real-world data, to enhance the inclusion of underrepresented groups in clinical research studies.

# Understanding the scope of the problem

Inclusivity is a key factor in clinical trials, to ensure that research findings are representative of the population and applicable to all patients, who may eventually receive the treatment. Clinical trials involve testing new medications, therapies, or medical devices to determine their safety and effectiveness. However, a lack of inclusivity in clinical trials can have negative consequences and hinder the progress of medical research.

The INCLUDE project examined underrepresentation in clinical design and delivery, and identified a range of underserved groups, and highlighted common barriers to participation. The project identified key groups such as older people, ethnic minorities, and women who continue to be underrepresented in clinical trials today [1].

# Implications of underrepresentation

The involvement of women, ethnic minorities, and older adults is essential to the scientific, economic, and ethical value of clinical trials. Failure to include such individuals can lead to under diagnosis, undertreatment, and a lack of understanding of how certain medical therapies may affect specific groups of people.

For example, clinical trials investigating treatments for ischemic heart disease (IHD) often exclude older individuals despite their higher susceptibility of developing the disease [2]. To assess whether a drug is safe and effective for use by the elderly, a sufficient number of elderly patients are needed to be included in drug trials. Evaluation of the exclusion of elderly adults from 839 randomised controlled trials studying drug interventions for IHD concluded that, from these trials, 446 (53%) explicitly excluded elderly adults. The estimated proportion of participants aged 65 and older was 42.5%, and the estimated proportion aged 75 and older was 12.3% [2]. As such, these trials create challenges for treating clinicians in evaluating the risk benefit of medications in their older patients.

Physiological variations can translate into differences in pharmacokinetics and/or pharmacodynamics for specific drugs, meaning that medications can work or be processed differently in people of different sexes [3]. For example, the medication Dofetilide was approved by regulators in 1999, to help control irregular or fast heart rhythms (atrial fibrillation). Despite this, it was only in 2018, that a subsequent study found that the recommended twice daily dose was too high in over half of female participants, as they developed other abnormal heart rhythms and had an increased risk of cardiac arrest. This study highlighted the importance of having adequate representation of women in trials, as in the original phase III DIAMOND study, females constituted less than a quarter of all trial participants [4], clearly demonstrating the serious consequences of underrepresentation in clinical trials.

There have been several studies suggesting that pulse oximetry may not be as accurate in certain populations, particularly in individuals with darker skin pigmentation, including those of black ethnicity. This discrepancy in accuracy could result in an overestimation of oxygen saturation levels. The lack of diversity in the patient populations studied in clinical trials has been identified as a contributing factor to this issue. Consequently, there is a growing call for prospective studies to investigate the impact of ethnicity on the accuracy of pulse oximetry to ensure care is optimised for all [5].

These examples highlight the major consequences of not adequately representing these diverse groups in clinical trials, resulting in a lack of understanding of the drug's true impact, leading to potentially harmful consequences for those affected.
The Food and Drug Administration (FDA) recognises that some eligibility criteria have become commonly accepted by sponsors over time and used as a template across trials, sometimes excluding certain populations from trials without strong clinical or scientific justification (e.g., older adults, those at the extremes of the weight range, those with malignancies or certain infections such as HIV, and children) [6].

Exclusion of these populations from clinical trials not only propagates inequalities in healthcare but, also puts these groups at higher risk of experiencing adverse effects to medical interventions once they have reached the market.

## Why is there underrepresentation in clinical trials?

Despite the collective understanding across the industry to the value of inclusivity and diversity in clinical trials, underrepresentation remains a key challenge today.
This issue is complex and due to multiple reasons, involving systemic barriers, such as unequal access to healthcare and financial constraints, that can hinder the inclusion of individuals from disadvantaged backgrounds. Those individuals on lower incomes often face the responsibility of the care burden, such as looking after children or elderly relatives whilst working, which makes study participation more difficult [7]. Additionally, caregiving commitments shouldered by many women, often mean they lack the time to participate in research.

Recruitment strategies and trial logistics can pose significant barriers to trial enrolment and retention. For example, recruiting through tertiary centres located in urban areas, far away from rural populations, can make enrolment in this group challenging given the structural barriers and transportation issues [1]. Additionally, studies have found that failing to provide transport for individuals with limited mobility, or even translating study information for those who cannot read a given language, can further hinder recruitment efforts [8].

Other barriers include lack of willingness to participate or a lack of awareness among certain populations about research opportunities, as well as mistrust by some individuals in medical research. The legacy of historical and contemporary abuses in medical research is an important factor in the lack of engagement in both healthcare and research, and careful consideration needs to be made when developing recruitment strategies and patient materials [9].

Another key reason for underrepresentation in clinical trials is the limitations of the study design. Clinical trial design tends to be conservative, often excluding minority groups such as the elderly or those with complex medical histories due to safety concerns and the desire to ensure favourable outcomes. Additionally, physicians' perceptions and biases can influence the types of patients they consider to be suitable for participation into trials, older individuals may be perceived as more vulnerable or less likely to be able to tolerate new therapies, and therefore these patients are excluded from participation in trials even when not explicitly excluded in the protocol [10]. Implementing safer trial methodologies, and advancements in technology could potentially address these limitations and allow the inclusion of a broader range of patient populations, thereby improving the generalisability and applicability of study findings.

## Addressing challenges and regulatory oversight

Despite recognition that this problem exists, attempts to address these complex issues have had minimal impact. Different areas of research have different barriers to engagement to overcome and therefore there are no easy solutions, and a tailored approach is required. Nevertheless, there will be some common generic actions that would help address some of these issues. To achieve accurate and meaningful research outcomes, it is critical to evaluate improvements in trial design, particularly inclusion and exclusion criteria, which often lead to the underrepresentation of minority groups. Encouragingly, steps aimed to address this issue are underway. For example, the UK Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA) are working on a new guidance document to help support researchers. This guidance will encourage researchers to consider who will benefit from the research and how to include them, particularly individuals from marginalised populations who are frequently underrepresented or excluded [11].

The UK's proposed approach will go beyond the requirements currently in place in the US. While the FDA focuses its diversity plans on enhancing underrepresentation of racial and ethical populations, the HRA, who are responsible for overseeing ethics committees in the UK, will have a broader scope, encouraging sponsors to take a holistic approach to inclusion.

Improving diversity was also high on the agenda of the review undertaken by former health minister Lord O'Shaughnessy to improve the state of commercial clinical trials in the UK. The report highlighted several points in which the country could improve commercial clinical trial operations, including leveraging technology to enable a more diverse cohort of patients to be invited to take part in clinical trials, and making research more convenient, thereby allowing people to take part from the comfort of their own homes [12].

While regulatory bodies play a significant role in setting legislation and creating guidelines, sponsors of clinical trials also have a crucial role to play in improving inclusivity and diversity. One of the most effective strategies is community engagement. By involving patients and the public in the research process from the outset, sponsors can gain valuable insights to help improve and inform study delivery, as well as gaining a better understanding of the patient's needs and potential barriers to participation. This engagement helps build trust, increase awareness, and ultimately, encourage greater participation from underrepresented populations.

Addressing the logistical burdens of trial participation must become a key consideration for sponsors, designing trials based on lifestyle factors such as work commitments, childcare and caregiver needs are strategies which will help improve the recruitment of minority groups. Reducing the frequency of study visits, considering flexibility in visit windows, and the use of electronic and digital health technology can help to streamline trial procedures, making trials less onerous, and potentially appealing to a broader range of individuals.

# Solutions and future outlook

Decentralised clinical trials (DCTs) using real world data sources are becoming an increasing part of the clinical trials landscape. In the recent government response to Lord O'Shaughnessy's independent review into commercial clinical trials in the UK, it recommends using innovative methods to delivering studies closer to where people live, including virtual studies and decentralised approaches [13].

The adoption of decentralised models, and the use of routinely collected data from patients' electronic health records (EHRs), can provide important evidence on the safety and effectiveness of new drug therapies. DCTs allow participant's to engage remotely and access research opportunities closer to home, rather than a traditional tertiary centre. These alternate locations can include their local GP practice, or pharmacy, mobile research units, or even visiting the participants home for those who may be medically complex, and/or house bound. Making trials more accessible and removing the travel burden, will help facilitate participation of more diverse patient populations within the community setting where their day-to-day care is delivered.

Using real world data sources enables richer, more comprehensive datasets to be collected, leading to deeper insights and more robust data analysis. The use of data direct from source allows access to real-time data streams, meaning researchers can monitor patient outcomes and safety continuously throughout the study. This has a key advantage over more traditional methods of capturing safety data, as the integration of multiple healthcare data sources allows for more comprehensive and accurate data to be collected, and the ability to monitor patients' safety long-term in post-trial follow-up.

Such active surveillance technology was used in the Salford Lung Studies, two industry-sponsored, late-phase randomised controlled trials (RCTs), that were the first in the world to evaluate the effectiveness of a pre-licence medicine in a real-world setting. In comparison to traditional Phase III COPD trials, the Salford Lung Study (SLS) had a higher rate of overall Serious Adverse Events (SAEs), (27-29% vs 13-24%) and a higher rate of pneumonia SAEs (7% vs 1-3.2%) [14]. The higher rate of SAEs detected during SLS, compared to traditional trials demonstrates the effectiveness of using real-world data sources and innovative technology to significantly enhance patient safety and produce much richer datasets for analysis.

# Conclusion

In conclusion, addressing the issue of underrepresentation in clinical trials is critical to ensure that the research findings are representative of the entire population, to promote equity in healthcare, and improve patient outcomes.

Despite the collective recognition of the importance of inclusivity and diversity in research, significant challenges persist. However, proactive efforts are underway to overcome these barriers and promote greater inclusivity in clinical trials.

The adoption of innovative solutions, such as community engagement, DCTs, and the use of dynamic safety monitoring, with real-world data taken directly from the source, holds immense promise in enhancing diversity and improving the representativeness of research findings.

In the future, continued efforts are still needed to address systemic barriers, reduce underrepresentation, promote equity in access to research opportunities, reduce risk in underrepresented populations, and ensure voices of all patients are heard and represented in clinical research.

# A technical solution to help improve inclusion in clinical trials

ConneXon is a validated electronic data capture system that collects study data direct from participant Electronic Health Record (EHR). Collecting data in this way, direct from source, enables near real time monitoring of participants with customisable safety alerts to help safeguard their wellbeing while participating in a trial. Safety monitoring with ConneXon allows researchers to detect adverse events and other safety issues as soon as they occur. Unlike other methods that rely on participants reporting issues themselves, ConneXon alerts the research team within 24 hours of an event being recorded in the patient's EHR, allowing swift action at the earliest indication.

## How does ConneXon help improve inclusion?

ConneXon enables fully decentralised clinical trials allowing individuals to participate through their local GP or from the comfort of their own homes. This means, for example, people with mobility issues, or living in isolated areas are able to participate with minimal interaction. Connexon's active surveillance technology is proven (14) to be a faster, more accurate method of AE detection, allowing higher risk cohorts of patients to be enrolled into trials leading to more comprehensive and representative study results.

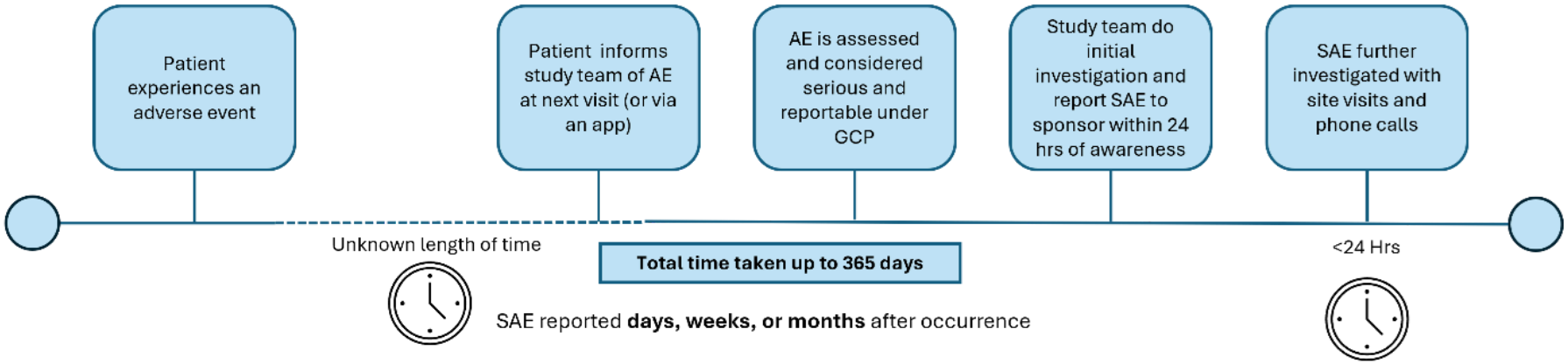
This means researchers can broaden their study protocols to include participants that may have been previously excluded, with the confidence they can quickly react to safety issues while better assessing the risk-benefit profile of a drug throughout the clinical trial, and beyond into post market surveillance phase.

# ConneXon SAEfe - A quantum leap in safety reporting

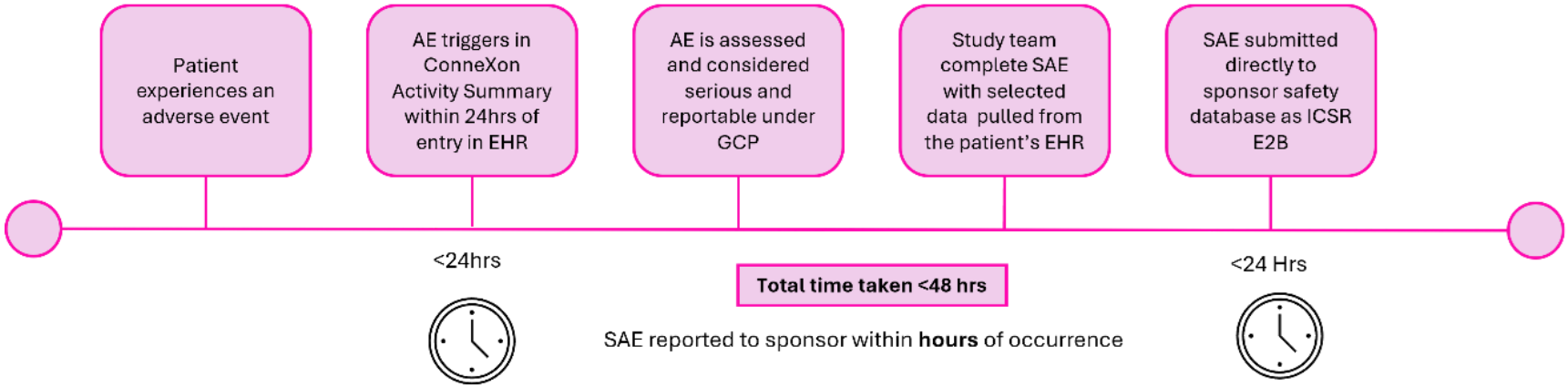
ConneXon is a gold standard in clinical trial safety monitoring. Now with its new SAEfe system feature, it offers researchers a unique end-to-end safety monitoring and reporting system that can provide up to 70% saving in the costs associated with SAE reporting.

SAEfe seamlessly populates SAE reports with data directly from the participant's EHR record. Additional relevant medical conditions and other pertinent information can be easily selected using the SAEfe system and added to the SAE report. Adhering to ICH GCP standards, once a completed SAE report is saved, it is electronically submitted, using E2B messaging, as an Individual Case Safety Report (ICSR) straight to the sponsor study database. This streamlined process reduces transcription errors, enabling researchers to redeploy the time saved to focus on the wellbeing of participants.

## Traditional safety reporting




## ConneXon SAEfe reporting system



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