Ten years on, the pioneering Salford Lung Study continues to influence modern thinking for real-world evidence and pre-market approval of pragmatic clinical trial design

GlaxoSmithKline plc (GSK), the industry sponsor of the Salford Lung Study (SLS), took the bold decision to pilot a new trial model.

In a ground-breaking move, the company compared the effectiveness and safety profile of initiating asthma and chronic obstructive pulmonary disease (COPD) treatments in a trial that used a diverse, real-world patient cohort, carried out in an everyday primary care setting.[1]

Professor Martin Gibson

Professor Martin Gibson is Chief Medical Officer at NorthWest EHealth (NWEH) and Director of the NIHR Clinical Research Network for Greater Manchester. Prof. Gibson is a consultant physician specialising in diabetes and lipid diseases at the Northern Care Alliance NHS Foundation Trust, where he formerly served as Research & Development Director for both the acute and primary care trusts. His involvement in many clinical trials led to his interest in the ability of electronic clinical data systems to enhance medical and pharmaceutical research.

Professor Nawar Bakerly

Professor Nawar Bakerly is a Consultant Respiratory Physician and the Chief Clinical Information Officer (CCIO) at Salford Royal Foundation Trust in Greater Manchester. Prof. Bakerly also works as an academic and honorary senior lecturer at the University of Manchester and has participated as a lead or co-investigator in many clinical trials, including the SLS for asthma and COPD. Prof. Bakerly's areas of expertise focus on real-world evidence (RWE), pragmatic randomised clinical trials (PRCTs), and the use of digital technologies in improving clinical research.

Claire Williams

Claire Williams is Head of Pharmacovigilance and Regulatory Services at NWEH and a founder member of the team responsible for devising and implementing the SLS. As Safety Lead for the study, Claire led the development of the real-time patient safety monitoring, and reporting technology and supporting processes, which were fundamental to the success of the SLS. With a Master's Degree in Pharmacovigilance, Claire is an expert member of the Central Greater Manchester Research Ethics Committee and national Fast Track Research Ethics Committee.

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A new paradigm in clinical trials

Early in the 2000s researchers were starting to ask questions about the validity of relying solely on randomised clinical trials (RCTs) as evidence for the regulatory approval of new drugs.

The traditional RCT was acknowledged as the most reliable way to test the efficacy of a new drug, but the launch of the GSK-sponsored SLS on 13 March 2012 – the pioneering Phase III PRCT in asthma and COPD – was the start of a major paradigm shift.

For the first time, the SLS generated evidence of a new drug's effectiveness in a large, real-world patient cohort. The study design allowed for broad patient recruitment, accurate data collection to inform implementation in routine clinical practice, and a robust system to identify and record adverse safety events.

In this case study, we talk to Prof. Martin Gibson, Prof. Nawar Bakerly and Claire Williams, three of the original members of the SLS team. They reflect on some of the challenges in study design and trial delivery that were overcome by the SLS – and discuss how the principles of RWE, community clinical implementation and PRCTs that were established in the study have influenced today's thinking, heralding a move towards a blended strategy of RCTs and PRCTs in pre-market regulatory approval programmes.

"It's impossible to underestimate the impact of the SLS. Even now, more than 10 years on, we regularly get asked about some element of the study or are told how the work we carried out has influenced a trial design in progress today."

Prof. Nawar Bakerly, Salford Royal NHS Trust.

"What we achieved was truly ground-breaking – and still is. The SLS set a precedent for safety monitoring and reporting in clinical trials and is upheld as a model of excellence today."

Claire Williams, NWEH

A new randomised clinical trial model

For more than 60 years, the pharmaceutical industry has relied on RCTs as its key model for collecting data regarding the safety and efficacy of a new drug substance to present to the regulatory authorities that approve new drugs for use.

Much has been written to chart the history of RCTs.[1] Designed to be performed in a rigorously controlled setting that minimises unwanted bias and offers independent proof of the efficacy of a new treatment, RCTs look to make a comparison with either a placebo or existing therapeutic best practice.

The somewhat artificial structure of RCTs, with closely defined patient cohorts under intensive clinical management, means that they are not only inherently time, labour and cost intensive, but also may not reflect a true-to-life environment. Prof. Bakerly reinforces this point: *"Importantly, the validity of the data from an RCT may not reflect a real-world setting, where the dynamics of clinical care are significantly different compared with the controlled environment of a trial."*

Prof. Gibson concurs: *"For most new treatments, the evidence from RCTs at the point of market approval is insufficient to fully guide decisions by physicians and policymakers as they look to select the best treatment for patients in routine clinical practice."*

A real-world picture

In contrast, trials that collect data in the routine clinical setting – known as observational, real-world, or PRCTs – set out to overcome some of the restrictions of traditional trials and offer a new perspective based on RWE of the relative effectiveness of a treatment.

Prof. Gibson comments: *"Before the SLS, PRCTs were considered to play an important role in post market approval surveillance or for the collection of specific health economics data."*

More recent papers, however, have focused on the potential of an expanded role for the PRCT, with a 2019 review[2] noting RWE studies can play a role in:

- Assessing safety and effectiveness in real-world populations for regulatory purposes
- Comparing clinical outcomes in real-world observational trials of clinical interventions to determine optimal treatment strategies
- Identifying prescribing patterns for drugs with similar indications for population health analyses
- Measuring resource utilisation by patients in the real world; published papers compare economic outcomes in real-world observational trials to determine the most economically attractive treatment strategies

The regulatory authorities journey

For this potential to be realised, however, regulatory bodies around the world needed to come on board with PRCTs.

Although the debate continues today, regulators are offering a view of the way forward that is increasingly aligned with the needs of pharmaceutical companies, policy makers, payors and healthcare economists, amongst others.

Prof. Gibson notes: *"At various stages of the SLS and following the completion of the trial, various team members presented to the Food and Drug Administration (FDA) and other regulatory bodies with the goal of highlighting the insights the SLS provided, and how the concept of real-world trials could contribute significantly to the approval of a new drug therapy."*

The 21st Century Cures Act,[3] passed in the US in 2016, placed additional focus on the use of real-world data (RWD) to support regulatory decision-making, including the approval of new indications for approved drugs. It stimulated a lively debate on how best to utilise RCTs and PRCTs throughout the drug development process. More recently, work published in late 2020 by a group that included researchers from the pharmaceutical industry, clinical institutes and universities discussed the need to develop hybrid trial methodologies combining the best parts of RCTs with studies that generate RWE to provide adequate scientific evidence for regulatory decision-making.[4]

Enabling an inclusive patient population

The ground-breaking approach to the pharmacovigilance strategy played a fundamental role in the trial's success. Enabling typically excluded patients to take part in the trial, including the elderly and people who smoke, for example, required a dedicated, failsafe and round-the-clock patient safety monitoring programme.

Ms. Williams comments: *"By allowing a diverse patient population in a real-world setting, we anticipated there would be more safety events than in a typical RCT, which would need to be closely monitored and reported back to GSK. We were expecting high volumes of safety data and were using safety technology that had never been used before to generate safety alerts in near real time, allowing a rapid response."*

The comprehensive and accurate data generated allowed GSK to identify safety signals more quickly than in a traditional trial, with important risk-benefit analysis data made available for regulatory submission.

Data-driven decision making

The shift in the stance of regulatory bodies around the world has been instrumental in driving change – enabling drug developers to think outside the box of RCTs and incorporate elements of RWD and RWE in pre-market approval workstreams.

The FDA has issued guidelines to industry on considerations for the use of RWD/RWE[5] and papers have been published[6] that highlight work to develop hybrid trial methodologies that combine the best parts of traditional RCTs with observational study designs, to produce RWE that provides adequate scientific evidence.

In May 2022, the results of an FDA-funded initiative that studied how well RCT evidence could be duplicated by RWE/RWD were presented at a meeting in Washington DC, USA. A report at the time[7] highlighted the view of Harvard Medical School Professor of Medicine Sebastian Schneeweiss, one of the project leaders, who believed that the project addressed several misunderstandings about the role of RWE. He set out that RWE complements evidence from RCTs and does not replace it, and that every RWE study does not need to emulate an RCT, strongly suggesting that the value of RWE is in complementing RCT evidence.

This project is seen as a significant first step for the FDA to make good on its goals to provide industry with the best guidance on integrating RWE into clinical trial design and practice.

A similar evolution has occurred elsewhere in the world with, for example, the Medicines and Healthcare Products Regulatory Agency (MRHA) in the UK conducting a consultation exercise in 2021 and publishing in 2022 two comprehensive guidance documents:

- MHRA Guidance on the use of Real-World Data in Clinical Studies to Support Regulatory Decisions[8]
  - This provides an introduction to the MHRA's RWD guideline series, and points to consider when evaluating whether a RWD source is of sufficient quality for the intended use.
- MHRA Guideline on Randomised Controlled Trials using Real-World Data to Support Regulatory Decisions[9]
  - This provides points to consider when planning a prospective randomised trial using RWD sources with the intention of using the trial to support a regulatory decision. The guideline covers clinical trial authorisation and clinical trial design including choice of endpoints and safety data requirements.

In addition, at the end of 2021, the European Medicines Agency (EMA) outlined its vision of *"Enabling the use of RWE and establishing its value for regulatory decision-making on the development, authorisation and supervision of medicines in Europe by 2025."*[10] At the same time, the EMA announced the creation of the Data Analytics and Real-World Interrogation Network (DARWIN EU), an EU-wide network that will allow access to and analysis of healthcare data from across the EU. This was supported by two articles[11, 12] on the transformation to data-driven regulatory decision-making.

Key learnings from the SLS

The SLS is a set of two PRCTs – one in adult asthma patients, the other in patients with COPD.

In the asthma study, the trial evaluated the clinical effectiveness and safety of once-daily fluticasone furoate (100 µg or 200 µg)/vilanterol 25 µg in a novel dry-powder inhaler, versus existing asthma maintenance therapy. The study was initiated before this investigational treatment was licensed and conducted in real-world clinical practice to consider adherence, co-morbidities, polypharmacy, and real-world factors.

In the COPD study, a controlled effectiveness trial was conducted in a general practice setting – patients with COPD were randomised to receive either a once-daily inhaled combination of fluticasone furoate at a dose of 100 µg and vilanterol at a dose of 25 µg (the fluticasone furoate-vilanterol group) or to receive usual care.

This pioneering work was placed in Salford because of the well-developed infrastructure of integrated electronic health records (EHRs). The study relied on bespoke feasibility software, Feasibility Assessment and Recruitment System for Improving Trial Efficiency (FARSITE), developed by NWEH and securely hosted within the NHS network, which integrated the EHRs of consenting patients across all of their everyday interactions with GPs, pharmacists and hospitals. NWEH's electronic data capture (EDC) system, the Linked Database System, a forerunner of the NWEH ConneXon platform,[13] was instrumental in the trial's success, with data capture directly from source and a close to real-time safety monitoring system.

This highly developed linked database system allowed:

- Community-based population screening, feasibility assessment, patient consent and recruitment
- Close monitoring of patient safety in near real-time, with minimal intrusion into their everyday lives

Real time safety alerts

Before the introduction of the ConneXon platform into the trial, adverse event (AE) reporting was a limiting factor in the success of a community-based trial, restricting the recruitment of a broad patient demographic. The most common method, passive surveillance, depends on patients electing to report AEs, which can be unreliable. The ConneXon real-time monitoring system enables remote monitoring of patient EHRs to generate an alert in the instance of a serious adverse event (SAE) and prompt a clinical review, reducing the resource burden of more traditional SAE detection and increasing safety for trial participants, high quality data and shortened trial timelines.

Looking ahead

The consensus has emerged throughout all stakeholder groups that RCTs and RWD/RWE collected through PRCTs should be integrated throughout drug development.

A key driver has provided the practical means to make progress, namely the availability of comprehensive EHRs in combination with the interrogative technology, in particular the development by NWEH of a new, robust approach to patient safety monitoring.

With the pace of drug discovery already being accelerated by large public databases such as the UK BioBank and the Human Cell Atlas, the increasingly detailed healthcare records that can include information from a broad range of sources such as patient registries, health care databases, patient networks, social media, and patient-generated data from wearable technology, together with regulatory scrutiny, have emerged as a new tool in the pre-market regulatory approvals process. The role of the PRCT has achieved new significance.

Prof. Gibson sums up: *"Looking back, the SLS really did set the scene for what has followed – it has been incredibly rewarding to see the impact our work has made. Searching the U.S. National Library of Medicine Database recently, I noted around 3,500 real-world trials and 1,800 pragmatic clinical trials were listed at various stages of completion."*[14]

Ms. Williams notes: *"We are seeing a widespread industry move towards exploring the inclusion of a drug's target population in a clinical trial and, at NWEH, we are working with the Health Research Authority and Research Ethics Committees to support this. Using the learnings from the SLS, the goal is to implement a clinical trial model that facilitates a safe and practical methodology of ensuring a diverse and inclusive patient population in a real-world trial setting."*

Prof. Bakerly adds: “GSK made a bold move. Adopting this new approach of using new technology was ground-breaking in the pharmaceutical drug discovery environment, where the pace of change is typically slow. Whilst we believed what we were doing was important to the case for the new therapy, we couldn’t have predicted its landslide success. The broad-reaching outcomes of the SLS continue to influence trials today.”

Best practice in feasibility

NWEH’s technology platform, FARSITE, is a powerful feasibility tool to search, find, and recruit participants from primary care settings into clinical trials, whilst still preserving their confidentiality. In this trial, all patient recruitment was completed using this technology.

Increasing patient safety

The NWEH ConneXon clinical trial platform provides a secure, validated, and modular system to accelerate trials whilst increasing patient safety. ConneXon comprises a full EDC system, with data capture directly from source, plus a configurable electronic case report and a close to real-time safety monitoring system. This, together with parallel delivery of data for effectiveness and efficacy, allows the platform to be configured to the needs of each individual study. In this trial, ConneXon was utilised for data collection and remote patient safety monitoring with minimal intervention, thereby reducing patient visits and maintaining real-world conditions for participants.

A widely reported trial

The SLS is a ground-breaking study, evidenced by the volume and spread of publications reporting on all aspects of the trial. Discussions about the study design, systems and technology used as well as the outcomes of the study have resulted in 19 manuscripts being published and 51 congress abstracts being presented and/or published (as at October 2022). A bibliography detailing peer-reviewed papers, conference posters and other publications is available at **nweh.co.uk**

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True-to-life clinical trials

NWEH provides the pharmaceutical industry with a holistic approach to clinical trial design and delivery, helping bring drugs to market faster. FARSITE has the potential to streamline the complex processes associated with conducting trials in a regulated environment, affording the opportunity to bring life-saving therapeutics to the market quickly and efficiently.

NWEH is a leading figure in the field of electronic health record (EHR)-enabled randomised clinical trials. NWEH built the technology behind the success of the pioneering Salford Lung Study and is the only organisation in the world to have evaluated the safety and effectiveness of a pre-licence medicine in a real-world setting.

From feasibility studies and trial design to clinical delivery and data analysis, NWEH supports the success of pharmaceutical companies and contract research organisations across the globe.

To find out more about the NWEH true-to-life approach to clinical trials and how the company's tools and expertise in recruitment, design and feasibility, clinical management and delivery, safety data reporting, and data analysis could be applied to future projects, visit nweh.co.uk.

NWEH WEBSITE

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