Accelerating clinical trials: time to turn words into action

Invited commentary

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In a post-pandemic world where health systems around the world struggle, high quality randomised clinical trials are more essential than ever to ensure that the limited resources available are used most efficiently to deliver effective interventions. They provide a sound method to understand whether, how well and for whom health interventions are effective and needed to inform regulatory licensing, health care policy, and individual clinical care.

At no time was this more evident that during the COVID-19 pandemic. When the world confronted the challenges of a new disease, we saw the best and the worst of responses. Some 'treatments' were widely deployed amid much hype, many small trials were started (an unhelpful distraction),[1] and yet a few, large randomised trials succeeded in delivering results that saved hundreds of thousands of lives.[2-4]

For example, the RECOVERY trial assessed multiple generic, repurposed, and new drugs.[5] It was established at speed (with the first results being available within 100 days of the protocol submission), designed to be practical and accessible for patients and healthcare staff (making it a component of clinical care), and made good use of a wide range of routinely collected healthcare data. [6] This was practical randomisation in the real world and consequently produced evidence that

was directly relevant to that same real world. As senior FDA leaders have written, “Streamlining and quality are not opposed”.[6]

But the need for efficient randomised trials is not confined to the urgency of a pandemic.[7] A recent government-commissioned report by Lord James O’Shaughnessy has highlighted that far from the facilitatory, outcome-focused approach of the pandemic, the UK clinical trials ecosystem is currently mired in bureaucracy, dither and delay.[8] Commercial clinical trials activity dropped by 44% between 2017/18 and 2021/22, clinical trial start-up time (from application to MHRA to first participant dosed) was around 250 days even before the pandemic, and the proportion of patients recruited into clinical trials is just 2% (half that in Poland and Germany).[8]

Lord O’Shaughnessy’s report highlights 8 major deficiencies, which could be summarised as follows: too slow, too low priority, too low profile, too conservative. With a few notable exceptions (featured in the report), there is a clear tendency to head back to the comfort of (cumbersome) business as before rather than learn from what was so successful in the pandemic and embrace the possibilities of advances in medical, communications, and data technology allied to new forms of partnership involving patients, clinicians, the NHS, and the academic, commercial and non-profit sectors.

Lord O’Shaughnessy’s report includes 27 recommendations with the principal ones aimed at improving the speed and quality of initial trial authorisation by the MHRA, developing a coordinated pan-NHS contracting mechanism (reflecting the huge success of the UK’s single ethics approval process coordinated by the Health Research Authority), increasing the quality of data collected about clinical trials performance, improving patient access to clinical trials, and establishing a set of clinical trial acceleration networks aligned with the NHS and UK Life Sciences priorities.[8]

There is no lack of enthusiasm for clinical trials (commercial or otherwise) among health professionals and, most importantly, the public. And there have been some recent stand-out successes such as the recruitment of 140,000 participants into the NHS-Galleri trial of early cancer detection in just 10 months.[9] It is one example of several examples in the report of imaginative partnership between commercial, non-profit, NHS, government and patient organisations that allows trials to be delivered quite differently. The government’s response was largely positive although the commitment to fund just 2-3 of the report’s recommended 8-10 flagship “clinical trial acceleration networks” is disappointing.[10]

A key issue that comes through loud and clear is the need for substantial improvement in the clinical trials regulatory ‘Good Clinical Practice’ guidelines and the way that they are implemented. We must recognise that over-burdensome demands or misplaced emphasis reduce the scale, relevance and

quality of evidence available for licensing and clinical decision-making. Consequently, many exciting medical technologies are never taken through to late-stage trials or are only applied to niche circumstances even though they might have an important role in preventing or treating common diseases. We need principles not pedantry – principles that will remain relevant in different contexts now and in the future, and which allow those designing and conducting trials to devise and deploy methods that best fit the circumstances (see box).[11] This is a global issue and we need to improve research quality through well-designed, well-implemented clinical trials to produce actionable evidence to address public health priorities across diverse populations. The International Conference on Harmonization has initiated a consultation on revised 'Good Clinical Practice' trials guidelines, which must be carefully scrutinised to ensure that it provides the necessary flexibility to allow thoughtful application of the key principles.[12] Meanwhile, the World Health Organization is developing guidance to strengthen the quality of clinical trials.[13,14]

New UK clinical trials legislation is promised, and it was encouraging that the government response to a public consultation on this topic was very positive.[15] It recognises the need for a more streamlined, agile, risk-based and patient-focused approach, one which welcomed innovative methods. However, the timing and content of the necessary legislative changes remains unclear.

Better legislation and faster review times will not be sufficient. It is essential that those charged with regulatory and governance responsibilities have access to the training and expertise needed to make sound, proportionate judgements in a world of methodological and technological change. There is substantial empirical and theoretical expertise in the wider academic, health, data science, clinical and patient communities which can readily add value to what might be called an Open Regulatory Science. The MHRA (and other regulators worldwide) would be wise to follow the example of the US FDA which established the Clinical Trials Transformation Initiative in 2008 to enable broad-based input into regulatory thinking.[16]

As Lord O'Shaughnessy himself writes, "no significant policy and behavioural change ever happened because someone published a report, and this is no exception." It is therefore imperative that the government support his recommendations and in turn make full use of the wider expertise and experience in clinical trials to deliver the necessary transformations. With a single-payer health system, strong academic and life sciences base, and supportive and interested population, the UK has an opportunity to demonstrate once more how efficient trials, carefully designed and appropriately regulated, can improve the health and prosperity of many. But the opportunities are not limited to the UK – a more agile, streamlined and efficient approach to clinical trial conduct, regulation and oversight globally would benefit public health worldwide.

Conflict of interest

MJL, RH and CR design and conduct clinical trials funded by grants to their institutions from the pharmaceutical industry, government and charitable organisations but have no personal financial interests in the pharmaceutical sector. MJL and RH receive part of their salary from Protas, a non-profit organisation that receives grant funding from multiple commercial, government, philanthropic and charitable organisations.

Box: Five Principles of Good Randomised Clinical Trials

The following 5 principles were developed by the Good Clinical Trials Collaborative[11] and focus on the unique strengths of randomisation while setting out the underpinning principles necessary to generate reliable results safely, ethically and efficiently. Results of good trials improve public health by protecting patients from inappropriate use of unsafe treatments and enabling access to effective treatments which substandard trials failed to identify. Good trials reduce research waste and build trust.

1. Good randomised clinical trials (RCTs) are designed to produce scientifically sound answers to relevant questions

This requires the combination of key design features such as proper randomisation to avoid selection bias, adequate sample size to minimize the play of chance, unbiased assessment of outcomes, and intention-to-treat analyses.

2. Good RCTs respect the rights, safety and well-being of participants

Ethical clinical trials combine seeking answers to important questions with scientific validity and appropriate protection and respect for all involved, particularly participants. Independent review through a Research Ethics Committee (REC) or equivalent, clear, accessible communication and relevant consent are at the heart of this principle.

3. Good RCTs are collaborative and transparent

All those involved in RCTs share responsibility for building and sustaining the trust of collaborating partner organizations and clinical communities, participants, and the wider public. Trust is undermined by lack of relevance or transparency, and lack of respect for of the rights and values of participants and those whose care will be influenced by the results).

4. Good RCTs are designed to be appropriate for their context

Ensuring that a trial is set up to be practicable and produce reliable, actionable results is an important scientific and ethical duty. Consideration of the context and existing resources in a proposed trial setting can better inform effective trial design.

5. Good RCTs manage quality effectively and efficiently

Delivery of a high-quality trial requires competent decision-making and coordinated execution. Focus should be on adopting risk-based proportionate approaches - identifying the key issues that would have a meaningful impact on participant well-being and safety or on decision-making based on the trial results.

The Good Clinical Trials Collaborative (GCTC) was established to develop and promote the unique benefits of RCTs across all contexts. These principles were developed by a wide range of individuals and organisations with relevant expertise, experience or interests, including those from regulatory agencies, biopharma, academia, non-commercial funders, health charities, ethicists, clinicians, patients and broader public, including those from higher and lower income settings.

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