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EDITORIAL

Clinical Studies

Revitalising cancer clinical trials: definitely time for patient-centred reform

Work is ongoing to recover UK clinical research capacity and capabililty post COVID-19 pandemic (https://sites.google.com/nihr.ac.uk/thefutureofukclinicalresearch/home), but many of the barriers investigators faced pre-pandemic persist. Taking a more patient-centred approach to reform may help apply lessons learned during the pandemic and facilitate 'building back better'.

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Following the ground-breaking development of effective treatments and vaccines for coronavirus disease 2019 (COVID-19) that occurred within months of the main pandemic hitting the UK, the Department of Health and Social Care (DHSC) signalled the need for clinical research to be embedded throughout routine healthcare. Several key policy documents were published in 2021 (https://sites.google.com/nihr.ac.uk/thefutureofukclinicalresearch/home, https://www.nihr.ac.uk/documents/best-research-for-best-health-the-next-chapter/27778), setting out a vision for expanding research opportunities in our health and care systems, as key drivers for improving care quality and efficiency, as well as saving lives.

However, delivering this bold research agenda remains challenging in practice: key themes including streamlining of R&D processes, rapid access to data and digital tools and provision of a robust research workforce have yet to materialise. As discussed in the review paper of Morton and colleagues [1], some of the major barriers to clinical research conduct are self-inflicted by our own research community. So, how did we get ourselves into this mess and how do we get ourselves out of it?

Good Clinical Practice (GCP; [2]) provides an international ethical and scientific quality standard primarily serving to protect the rights, integrity and confidentiality of trial subjects. It also harmonises processes associated with the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials. Reassuringly, GCP has underpinned the development of virtually all the cancer treatments in use today. However, while in the twentieth century, regulation of clinical trials was relatively light-touch, since the turn of the century when the European Union (EU) Clinical Trials Directive was introduced, the conduct of clinical trials has become one of the most highly regulated and intensively monitored of all activities undertaken within healthcare. While the EU Directive was intended to speed up patient access to new drugs and reduce cost to sponsors and to the public, the incessant layering on of more and more bureaucracy has meant that the cost of getting a new cancer drug to market has increased exponentially in the last 20 years and now stands at around $2-5billion [3].

The requirement for such high levels of scrutiny and administration has created an industry in itself, incurring huge costs in terms of manpower, as well as finances. At a time when the NHS is undergoing formidable stress, the pressures associated with undertaking clinical research are now causing major harm: R&D departments are grinding to a halt, research support staff are walking away and clinicians are becoming increasingly disengaged. Ironically, this comes at a time when development of novel cancer diagnostics and therapeutics is at an all-time high and the DHSC has embarked on a major partnership with Industry to boost research into cancer vaccines (https://www.gov.uk/government/news/new-partnership-to-boost-research-into-vaccines-for-cancer), bringing a programme of new trials as well as investment in science, training and education to the UK. Excitement for a new era of anticancer strategies has to be tempered with the very real limitations at ground level, where capacity is a major barrier to research delivery.

So, what are the key capacity pinch points that we need to be addressing? Morton et al. [1] and others [4] have used the pandemic experience to demonstrate where change needs to happen, identifying opportunities to reform all key components of research: the approvals process, site set-up, recruitment and consent, delivery of trial procedures and data handling. They recommend simplification of what have become hugely over-complicated systems. It was possible to fast track various regulatory hurdles, speed up approvals processes, strip down and modify COVID-19 trial protocols during the pandemic, which suggests significant redundancy, as these studies were still conducted in accordance with GCP and to the satisfaction of regulators responsible for approving new therapeutics for clinical use.

It is important to acknowledge the extensive ongoing work embodied within the UK Clinical Research, Recovery, Resilience and Growth programme, which focusses on 'building back better' post-pandemic (https://sites.google.com/nihr.ac.uk/thefutureofukclinicalresearch/home). Multiple interventions aim to release research capacity, do things differently and enhance the national reputation for delivering for Life Sciences. However, progress is slow and needs to go further and faster.

Would it help to put patients rather than process at the centre of our thinking? Let's for a moment reflect on the people whom all this regulation is supposed to be safe-guarding. Patients with cancer want access to state-of-the-art treatment at the earliest possible time. If they are going to choose a trial over standard of care, they need to know it will not delay starting their treatment,

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because time is of the essence. They want to understand what is going to happen to them if they take part in the trial and they don't want to feel that the burden of taking part in research is too onerous such that they reject participation. They want to feel safe during the trial and be fully informed of any potential risks. Most participants and their families would like to know the final results of the trial in which they partook. They would like to be reassured that their participation was not in vain - that the results were of use in some way and have contributed to future care of people with their condition. Common interpretations of GCP feel far from 'good' for patients. Its implementation has become a tick-box exercise, with regulators and monitors generating ever more boxes that must be ticked, while the impact on patients appears to have become overlooked. For fear of incurring negative inspection outcomes, sponsors have prioritised risk aversion over risk proportionality.

Investigators—arguably those closest to the research participants—may hold a key to reversing this trend. Some of the most successful COVID-19 trials (e.g. the RECOVERY trial [5]), were non-commercial sponsored, led by clinical academics in partnership with Industry. The value of strong clinical leadership is evident in comparatively brief protocols and patient information leaflets, focussed safety assessments and data collection requirements. Contrast these with the average commercial-sponsored cancer trial protocol which now generally exceeds 100 pages, with patient information leaflets often 30 pages or more, in length. As recommended by GCP and advocated by NIHR leaders [6], strong Chief Investigator and Principal Investigator engagement in protocol development and trial set-up can promulgate a sense of trust needed to reassure both sites and sponsors that a centralised, single sign-off model for site set-up is feasible (https://www.england.nhs.uk/aac/what-we-do/embedding-research-in-the-nhs/national-contract-value-review/). Research-active clinicians must be given sufficient protected time in their job plans to deliver this function.

The benefits of reform cannot be underestimated: protocols more closely mirroring routine care will ensure outcomes are more relevant to real-world populations; those adapted to post-pandemic ways of working facilitating remote consenting and virtual visits are much more likely to access underserved communities; information leaflets focussing on what patients need to know rather than what might protect a sponsor from litigation will increase recruitment rates and timely trial completion; risk-appropriate regulation should reduce the time commitments needed to set up and conduct many cancer trials, take pressure of an exhausted workforce and save on ever-soaring research costs.

The onus on our community now is not to go back to where we were pre-pandemic, but to seek to hold on to change and above all, to keep our patients at the centre of our thinking.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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