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Implementation of digital health technology in clinical trials: the 6R framework

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AstraZeneca has introduced digital health solutions into clinical trials, demonstrating improved patient experience, accelerated timelines and reduced costs.

Clinical trials usually follow a site-based model that is centered around in-person patient visits for recruitment, interventions, assessments and follow-up[1]. Although patients benefit from in-person contact, reliance on clinical visits can represent a large burden for many patients, who must navigate challenges due to the time, logistics and cost of attendance[2]. The use of digital technology has been proposed to address some of the potential inefficiencies associated with the site-based clinical trial model, with the broad aim of optimizing the experience of participants in clinical trials[3].

Digital solutions

The increasing access to, and familiarity with, digital devices across global populations has provided opportunities for greater efficiency and ease of clinical trial procedures. Electronic devices have inspired the development and utilization of digital biomarkers via both passive and active collection of patient-generated data, which can be collected remotely from a connected device, such as a smartphone, a clinical device or a digital wearable[3]. Home-based data collection enables more frequent measurements, resulting in greater precision and statistical power than traditional in-person monitoring schedules[4].

Remote patient monitoring provides many benefits to patients, including improvements in health-related quality of life, earlier detection of clinically actionable events (such as adverse events), improved patient compliance, and potential reductions in in-person visits to emergency rooms or duration of hospitalization. Ultimately, these benefits can enable patients to spend longer on treatment, thereby driving improvements in clinical outcomes, such as overall survival[5,6].

Over recent years, the availability of digital solutions that are relevant to the design and conduct of modern clinical trials has increased[7]. In particular, the COVID-19 pandemic has accelerated the implementation of digital solutions, which have challenged the traditional reliance on in-person contact. The digital innovation seen over the past few years has the potential to bring lasting improvements to current clinical trial design and delivery, maximizing benefits to patients and ultimately improving access to new investigational drugs.

A patient-focused approach

To improve the way we run clinical trials, we began by trying to understand patients' opinions and perspectives. We generated qualitative research from 322 patients, caregivers, and trial investigators from 9 countries (the USA, the UK, Germany, Sweden, Russia, China, South Korea, Japan and Poland) to understand their experiences of participating in clinical trials. In total, we conducted more than 280 hours of observation and discussion with patients in their homes, compiling 10,000 quotations. We used the information collected to identify opportunities to enhance patient and investigator experiences in clinical trials.

Between 2018 and 2019, we also reviewed 91 protocols across oncology, respiratory and cardiovascular diseases and concluded that 74–85% of the trial assessments could be successfully collected remotely using clinically validated devices; this could reduce the number of clinical physical visits by up to 40% (Fig. 1).

During 2020 and 2021, in response to the challenges posed by the COVID-19 pandemic, we accelerated our development of digital solutions, with the aims of facilitating patient and investigator access to clinical trials and to ensure trial continuation. Based on this experience, and working with patients, caregivers and trial investigators, we have consolidated the suite of potential digital solutions that will enhance the patient experience in clinical trials across therapeutic areas and updated the AstraZeneca 5R framework[8,9] for R&D productivity into a 6R framework (Fig. 1). Three examples can be used to demonstrate the value of the 6R framework.

Reduced clinic visits

The DAPA-MI trial, which was initiated in September 2020 to evaluate dapagliflozin in patients with myocardial infarction, incorporates several digital solutions (Table 1). The DAPA-MI trial is conducted in collaboration with the Uppsala Clinical Research Center (UCR) and the Myocardial Ischaemia National Audit Project (MINAP) in the UK.

The trial integrates routine care and registries. Registries are used by physicians to store patient health data collected over time, often during regular visits. For this study, data were pulled directly from the registry and study visits were aligned to standard of care, a pragmatic innovative approach that reduces patient burden and streamlines trial delivery for sites. We also, for the first time, implemented UNIFY, a bespoke digital platform for patients and investigators in clinical trials. The UNIFY platform provides an integrated user experience that connects the different digital solutions in a clinical trial, thereby reducing the administrative burden on patients and investigators. UNIFY enables secure, real-time transfer of data (collected remotely using the associated mobile phone application and medical devices) between patients and trial sites, in a single app for the patient and a single portal for the site, thereby resulting in the collection of substantially greater volumes of data than is possible during in-person visits alone. UNIFY enhances communication between patients and investigators, promotes adherence to study procedures and treatments, and improves patient access to medical information and support. We have also deployed AIDA, a bespoke artificial intelligence (AI) software, for the detection and

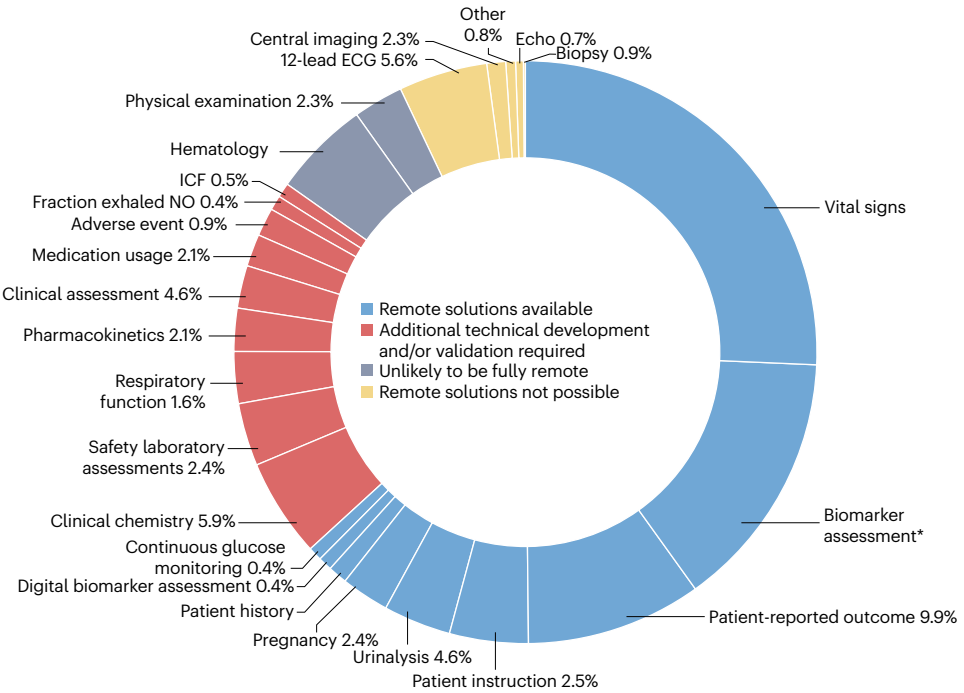

Fig. 1 | The feasibility of remote conduct for assessments in clinical trials. The number and type of in-person assessments conducted across 91 trials for various examination types were categorized by the feasibility of remote conduct. ECG, electrocardiogram; ICF, international classification of functioning, disability and health. *For biomarker assessments, home-based biomarkers or remote assays could be developed.

adjudication of events in cardiovascular trials. AI software may increase the quantity, quality and reliability of data generated from clinical trials that include patients with cardiovascular disease[10].

The DAPA-MI protocol enabled a 60% reduction in the number of study visits, compared with DAPA-HF, an earlier trial that did not include digital technologies, as well as a 60% improvement in patient experience (as measured by the patient experience index), compared with other similar trials.

A reduction in the number of in-person clinic visits can reduce the overall cost of the study. Based on current costing and the remaining estimated budget for the study, the total cost per patient is projected at US$12,826 in DAPA-MI, compared with a similar study cost per patient of $22,698 in DAPA-HF, representing a 43% reduction in cost that equates to a saving of more than $25 million.

Increased statistical power

Clinical trials of chronic obstructive pulmonary disease (COPD) usually evaluate endpoints that are based on either the frequency of moderate and severe disease exacerbations or the forced expiratory volume in 1 second (FEV_1). The substantial variability of the decline in FEV_1 between patients requires the use of large trial populations to evaluate treatment benefit[11,12]. Exacerbations are rare and trials are therefore long and enroll a large number of patients to provide sufficient statistical power for efficacy analyses[12]. The CRESCENDO trial, started in August 2022 in patients with COPD, includes several digital solutions to improve the efficiency of data collection and increase statistical power.

In CRESCENDO, the primary and key secondary endpoints are examined remotely with digital solutions (Table 1), including a smart spirometer, the UNIFY platform that enables virtual visits and spirometry at home with coaching, and ArtiQ.QC, a cloud-based AI solution used to perform real-time quality control of the spirometry to ensure high-quality data collection.

The digital solutions incorporated in CRESCENDO are expected to deliver several improvements compared with traditional COPD trials. Remote data collection can capture information more frequently than traditional clinic visits, reducing required treatment duration by as much as 50% (from 24 to an estimated 12 weeks), and reducing the number of in-person patient visits by 50%. Real-time quality control of spirometry data with AI is projected to reduce missing data from inaccurate reporting by approximately 5%, compared with clinic-based data collection. These innovations have reduced participant numbers from an estimated 604 (for an equivalent traditional trial) to only 288.

The use of digital solutions in CRESCENDO is predicted to lead to a 15% reduction in overall trial duration and a 32% reduction in costs, as well as an expected 68% improvement in the patient experience index.

Remote patient monitoring

In the first-in-human phase 2 TROPION-PanTumor01 trial, the efficacy and safety of datopotamab deruxtecan (Dato-DXd) was investigated in patients with advanced solid tumors, and was associated with a manageable safety profile at all doses investigated (4, 6 and 8 mg kg^{-1} once per 3-week cycle)[13]. Stomatitis (mucosal inflammation) is a common and clinically significant complication of anticancer therapy, occurring in 20–40% of patients receiving treatment for solid tumors and leading to inflammatory and/or ulcerative lesions. In the non-small-cell lung cancer cohort, 40–60% of patients who received Dato-DXd reported stomatitis (mucositis), most of which were low-grade[13,14]. Stomatitis can be mitigated by measures such as prophylactic

Table 1 | The effect of digital solutions in clinical trials

Therapeutic area and study	Digital solutions	Description	Impact
Cardiovascular: DAPA-MI	Digital patient registries	Digital patient registries collected information for the clinical trial. Data were pulled directly from the registry without duplication of data entry by site and reducing the number of visits in clinical trial to standard of care. For this study, Sweden (SWEDEHEART) and UK (MINAP) were used.	Number of visits were reduced to standard of care visits to match the data being collected by the registry. The DAPA-MI protocol requires four in-person clinic visits in the first 24 months, whereas the traditional DAPA-HF protocol required ten clinic visits in the same period.
	UNIFY: Digital clinical platform for patients and sites	Bespoke digital platform for patients and investigators to collect data remotely using one mobile app for the patient and one portal for the site, improving the overall experience in the trial. UNIFY can integrate different digital components such as patient support, electronic clinical outcome assessments, devices and remote patient monitoring.	The UNIFY platform allows secure, real-time transfer of data, which are collected remotely using the associated mobile phone application and medical devices or sensors, between patients and trial sites, in one single app for the patient and a single portal for the site. UNIFY allows the collection of substantially greater volumes of data than is possible during in-person visits alone. UNIFY enhances communication between patients and investigators, promoting adherence to study procedures and treatments and improving patient access to medical information and support, improving experience for the patient and the site.
	AIDA (AI software for the detection and adjudication of events in cardiovascular trials)	Bespoke AI solution, including three components. (1) The 'event sniffer' improves the detection rate of cardiac events via home monitoring using connected devices. Event sniffer geofencing algorithms make use of location data for medical facilities, preserving patient privacy while flagging potential medical facility visits or prolonged stays and confirming these directly with the patient via a custom electronic patient-reported outcome. (2) The 'event harmonizer' simplifies data extraction and processing of complex information from diverse sources, such as death certifications, hospital discharge reports, and device data. (3) The 'event classifier' consists of a set of algorithms trained using data from historical clinical adjudications, which can adjudicate or classify major adverse cardiovascular events, such as myocardial infarction, stroke, hospitalization due to heart failure and cardiovascular death.	Event adjudication manually can take between 4–5 months, owing to the transfer of information and human assessment of each case. With AI, the adjudication time can be reduced to 5 min, with a small number of cases escalated for further human review, reducing timelines and cost.
COPD: CRESCENDO	Digital primary and secondary end points	The primary endpoint is time to the first COPDCompEx event.	This facilitates measurement of the secondary endpoint (lung function) by spirometry at home.
	Spirobank: Smart spirometer	Medical International Research Spirobank Smart Spirometer.	Enables spirometry from home.
	UNIFY: Digital clinical platform for patients and sites	The smart spirometer was connected to the UNIFY mobile phone application via Bluetooth, enabling telehealth video coaching via the application. To reduce the burden of manual data input and to make the spirometer easier for patients to use, the mobile application automatically records peak flow data registered by the spirometer.	Improves patient and site experience; reduces complexity of connecting the different components; drives higher compliance; and increases statistical power due to additional data.
	ArtiQ.QC: Real time data quality control with AI	A cloud-based AI solution, ArtiQ.QC, is used to perform real-time quality control of the spirometry to ensure high-quality data collection.	Real-time quality-control of spirometry data with AI is projected to reduce missing data from inaccurate reporting by approximately 5%, compared with clinic-based data collection.
Oncology: TROPION-PanTumor01	Digital app for remote monitoring and prevention of adverse events	Mobile phone app to mitigate the impacts of stomatitis by reinforcing the importance of good oral hygiene and improving recognition of the signs and symptoms; tracking onset and evolution of mucositis by patient self-reporting; providing relevant guidance to enable self-management of less severe symptoms; and prompting relevant communication with the trial site if symptoms worsen.	Mitigation of adverse events, either by patient coaching or early detection and intervention. Reduced treatment discontinuation and better patient experience and outcomes.

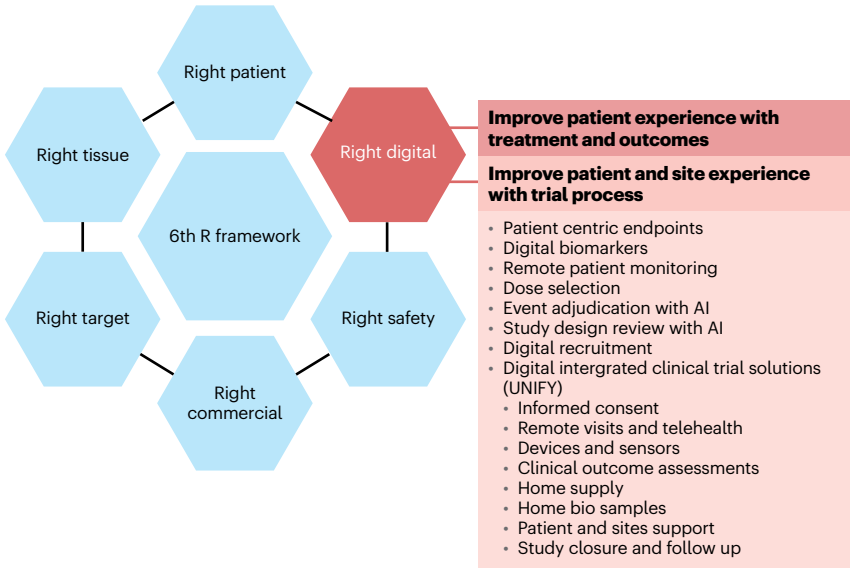

Fig. 2 | The sixth R. The 'right digital solution' has been added to AstraZeneca's framework for research and development.

mouthwash, and managing this toxicity may enable patients to remain on therapy for longer time periods, increasing drug exposure[15].

To mitigate the effect of stomatitis in new registrational trials of Dato-DXd, we developed a mobile phone application to mitigate the effects of stomatitis by: reinforcing the importance of good oral hygiene and recognition of the signs and symptoms; tracking onset and evolution of mucositis by patient self-reporting; providing relevant guidance to enable self-management of less severe symptoms; and prompting relevant communication with the trial site if symptoms worsen. Data are shared with site personnel in real time, including on the speed of onset of stomatitis, patient adherence to the oral care protocol, and providing insights on patients' risk of high morbidity, including risk of dehydration.

Integrated solutions

When we added digital solutions too late in the study design process, without a clear benefit to the study or change to the overall design, this resulted in a greater number of virtual visits, without a reduction in physical visits, increasing the amount of work for both patients and sites and resulting in higher complexity, time and cost.

A second mistake was to use separate digital solutions in the trial rather than integrating solutions into a single end-to-end user experience. In one study, for example, we used an external supplier, but each of their solutions was separate, resulting in six apps for the patient and six portals for the site. This brought increased complexity, poor experience both for patients and sites, and added time and cost to the study. It was for this reason that UNIFY was created. This digital solution integrates the different components (patient support solutions, eConsent, devices, remote patient monitoring, telehealth, bio samples and eCOAs) into one app for patients and one portal for sites, with a single sign on, and focusing on the user experience.

Digital health solutions in clinical research and development can enable a shift from the traditional physical site-based model, with gaps in data collection between visits, to a modern innovative design, with 74–85% of trial assessments potentially being collected remotely, reducing the burden on patients and trial sites, while at the same time leading to more continuous data collection, new end points and more innovative trial designs.

Digital solutions can deliver improvements in patient experience, accelerated study timelines, and reductions in cost. Improved data collection via digital solutions should enable the mitigation of adverse events, either by patient coaching or early detection and intervention. More proactive management of adverse events will reduce treatment discontinuation and ensure better patient experience and outcomes.

Given these successes with digital solutions, we have amended AstraZeneca's previously published 5Rs by adding 'the right digital solution' as a '6th R' (Fig. 2). Our recommendation to the wider clinical trial community is to consider the application of digital clinical solutions early in their study design, allowing more innovative methods of data collection, use of new end points, and remote patient monitoring.

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References

1. Thakur, S. & Lahiry, S. *Perspect Clin. Res.* **12**, 184–188 (2021).
2. Naidoo, N. et al. *BMC Med.* **18**, 6 (2020).
3. Inan, O. T. et al. *npj Digital Med.* **3**, 101 (2020).
4. Johannson, K. A. et al. *Eur. Resp. J.* **50**, 1602406 (2017).
5. Basch, E. et al. *JAMA* **318**, 197–198 (2017).
6. Basch, E. et al. *JAMA* **327**, 2413–2422 (2022).
7. Rosa, C. et al. *Contemp. Clin. Trials* **100**, 106219 (2021).
8. Cook, D. et al. *Nat. Rev. Drug Discov.* **13**, 419–431 (2014).
9. Morgan, P. et al. *Nat. Rev. Drug Discov.* **17**, 167–181 (2018).
10. Lea, H. et al. *Eur. Heart J.* **42**, ehab724.3061 (2021).
11. Vogelmeier, C. F. et al. *Respir. Med.* **173**, 106175 (2020).
12. De Soyza, A. & Calverley, P. M. A. *Eur. Resp. J.* **45**, 1692 (2015).
13. Garon, E. B. J. et al. *J. Thorac. Oncol.* **16**, S892–S893 (2021).
14. Spira, A. L. et al. *J. Thorac. Oncol.* **16**, S106–S107 (2021).
15. O'Brien, C. P. *Can. Fam. Physician* **55**, 891–892 (2009).

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Competing interests

C.O.D., M.B., E.B., R.H., S.G., C.M., A C., M.N.P. and S.G. are employed by AstraZeneca; E.H. is employed by Emmette Hutchison LLC. The authors declare no further conflicts of interests.