ELSEVIER

Decentralised clinical trials of investigational medicinal products

Abdel Douiri [1], Mohamed A. Alhnan [5], Muhammad Rizwan Asghar [13], Konstantinos Balaskas [9], Faiza Benaouda [5], John Bolodeoku [5], Clare Campbell-Cooper [22], Camille Carroll [3], Tao Chen [14], Keith Dorricott [6], Thierry Escudier [19], Carsten Flohr [10], Ben Forbes [11], Richard H. Guy [16], Stephanie Langouet [15], Anthony Lockett [5], Rayka Malek [1], Angela May [4], Graham R. McClelland [5], Sara M. Nasereddin [5,20], Alejandro J. Paredes [18], Sheuli Porkess [23], Eddie G.M. Power [2], Richard E.K. Russell [7], Richard Stephens [8], Heba Sailem [5], Daniel Sebastia-Saez [14], Matthew R. Sydes [12,21], John Weinman [11], Yunlong Zhao [17], Stuart A. Jones [5,*,§]

[1] School of Population Health and Environmental Sciences, King's College London, London, UK
[2] emPower Medical LLC, PA, USA
[3] Translational and Clinical Research Institute, Newcastle University National Institute for Health and Care Research (NIHR) Newcastle Biomedical Research Centre (BRC), Newcastle University, Newcastle, UK
[4] Bayer, 400S Oak Way, Reading RG2 6AD, UK
[5] Centre for Pharmaceutical Medicine Research, Institute of Pharmaceutical Science, King's College London, London SE1 9NH, UK
[6] Dorricott MPI, Pembroke Rd, Ruislip HA4 8NQ, UK
[7] School of Immunology and Microbial Sciences, King's College London, London, UK
[8] Patient Advocate, and Visiting Fellow, King's College London, London, UK
[9] Institute of Ophthalmology, University College London, London, UK
[10] St John's Institute of Dermatology, King's College London, London, UK
[11] Institute of Pharmaceutical Sciences, King's College London, London, UK
[12] Institute of Clinical Trials and Methodology, University College London, London, UK
[13] Department of Computer Science, University of Surrey, Guildford, Surrey, UK
[14] School of Chemistry and Chemical Engineering, University of Surrey, Guildford, Surrey, UK
[15] Centre for Pharmaceutical Medicine Research, Institute of Pharmaceutical Science, King's College London, London, UK
[16] Department of Life Sciences, University of Bath, Bath, UK
[17] Dyson School of Design Engineering, Imperial College London, London SW7 2BX, UK
[18] School of Pharmacy, Queen's University Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast, UK
[19] Pistoia Alliance, Wakefield, MA, USA
[20] College of Pharmacy, Amman Arab University, Mubis, Jordan
[21] BHF Data Science Centre, Health Data Research UK, London, UK
[22] Fortrea, Leeds, UK
[23] PM Life Sciences Consulting, Newbury, UK

* *Corresponding author. Jones, S.A. (stuart.jones@kcl.ac.uk)*
§ On behalf of the EPSRC-funded workshop on Engineering Solutions for Decentralised Clinical Trials held at King's College London, 28 Mar 2023.

https://doi.org/10.1016/j.drudis.2026.104676

Decentralised clinical trials (DCTs) can gather objective data in real-world settings through digital health technologies (DHTs) to obtain real-time measurements of clinical outcomes. However, such measurements remain infrequent in clinical trials of investigational medicinal products (CTIMPs). We review the decentralisation of CTIMPs, identify barriers to passive, real-time DHT use and recommend four solutions: a swift regulatory approval process for DHTs in clinical trials; development of specialised DHTs for CTIMPs; integration of human factors into DHT design for CTIMPs; and the adoption of data collection and transmission standards to enable decentralised CTIMPs to function effectively in patient homes.

Keywords: Decentralised; medicinal; digital health; remote; trials

Introduction

Decentralised clinical trials (DCTs) are trials "where some or all of the trial-related activities occur at locations other than traditional clinical trial sites".[p1] These trials can involve home visits by healthcare professionals, treatment provided outside conventional healthcare settings or the utilisation of digital health technologies (DHTs) to gather data from remote locations.[p1] Although various terms have been used to describe DCTs, such as remote trials, hybrid trials, tele-trials and others, all these terms focus on a key feature of this type of clinical research: the deliberate shift in operations beyond the usual trial site. The use of DHTs has become increasingly central to DCT execution because DHTs connect remote clinical trial activities back to the trial site, where data are collected, reviewed and stored securely.[p2] DHTs can gather trial data through active, time-limited activities, such as completing a questionnaire, or passive real-time data collection, for example continuous blood-pressure monitoring. Passive, real-time data collection in trials allows the full benefits of DCTs to be realised through authentic data collection with minimal patient burden. However, despite predictions that up to 70% of all clinical trials would include wearable sensors by 2025, an analysis of published DCTs shows that very few decentralised clinical trials of investigational medicinal products (CTIMPs), also known as investigational new drugs (terminology in the USA), incorporate DHTs for passive real-time monitoring.[p3] Although CTIMPs are only a small proportion of all clinical trials conducted, in 2023 <0.1% of the 4874 trials listed as decentralised on ClinicalTrials.gov were CTIMPs – they are important because they are required for the approval of new medicinal products.[p4] The absence of CTIMPs in the systemic reviews of DCT suggests that there are challenges to adopting DHTs in decentralised CTIMPs.[p5] To date, there has been little discussion about the challenges of using DHTs to collect real-time, passive data in decentralised CTIMPs and therefore this article aims to fill this gap.

Although the article emphasises CTIMPs, it also discusses work on pilot, mechanistic and observational studies where appropriate. It resulted from a multidisciplinary workshop that highlighted the challenges of decentralising clinical trials, attended by >120 members from the academic, industrial and regulatory sectors representing 30 organisations across clinical medicine, engineering, patient engagement, charities, clinical trial units, contract research organisations, national regulatory authorities, start-up firms and large pharmaceutical companies. The event was widely advertised as free to attend, and volunteers among the attendees formed writing groups that produced the final article. Most attendees had direct experience of DCTs from various perspectives: patients, trial leads, sponsors and coordinators. Key themes emerged from the recorded discussion sessions and presenter slides – these were grouped, rationalised and then contrasted with themes from published academic, clinical and regulatory literature. Limitations include potential enthusiasm bias, commercial influence and the challenge of capturing underrepresented opinions. To address these issues, we compared and contrasted the group's views with broader community evidence, using opinions and data from published literature to support or challenge the arising themes. Although performing systematic literature searches for each theme was impractical, we incorporated evidence from previous systematic reviews on decentralised trials and DHT use where possible, situating the work within the broader current landscape.

Opportunities for real-time data collection in decentralised CTIMPs

DCTs theoretically place the patient at the centre of the trial because they "can enable increased access to the appropriate patient population, reduce the patient burden to participate, generate augmented, more informed, objective datasets, increase engagement with the patient and gain a better understanding of the patient experience throughout the trial".[p6] These benefits seem to be innate to a DCT design, which reflects how patients now interact with their medical provider; that is, through various remote and face-to-face interactions. The pharmaceutical industry is playing a significant part in advancing tools for DCTs, creating new opportunities for decentralised CTIMPs. For example, AstraZeneca has reviewed >100 commercial devices from 60 vendors for potential use in future DCTs.[p7] Suitable devices have been piloted and shown capable of monitoring medication, blood pressure, heart rate, spirometry, respiratory rate, weight, ECG, lipids, ketones and other signals. However, a formalised approach to deploying these devices in CTIMPs has not been defined, and no completed studies have been published. Likewise, clinicians and DHT companies are collaborating to provide tools for DCTs. Several enterprises are developing (or have received approval for) innovative DHTs that enable patients at home to measure clinical outcomes for Parkinson's disease, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and other

conditions.[p8],[p9],[p10] Several of these technologies feature design characteristics that could help achieve the long-term goal of creating an economical, sustainable DHT platform for home use, integrating multiple sensors and devices into a comprehensive solution for real-time data collection across diverse clinical trials, including CTIMPs. Nevertheless, to realise these opportunities, more data are required to demonstrate that these systems meet the strict measurement validity and data security requirements in CTIMPs.

Systems are available to protect data generated in decentralised CTIMPs. For example, homomorphic encryption of data, which uses a cryptographic technique to safeguard data produced by DHTs in DCTs, offer a way to improve the current situation where data traffic, even when encrypted, is not fully secure.[p11] Furthermore, federated learning, a subset of machine learning, appears suitable for use in DCTs because it can apply training models across multiple decentralised devices or nodes, such as smartphones, without needing to transfer data to a central server. Federated learning also has the advantage of preventing data from being traced back to any individual site.[p12] These advanced data protection solutions integrated into decentralised CTIMPs can secure the transmission of trial-sensitive information when interacting with thousands of different data communication sites, which can be involved in a single study if the decentralised site is the patient's home.

DHTs that provide passive, real-time data collection offer the chance to incorporate artificial intelligence (AI) and other large language models (LLMs) directly into the trial data collection process. Using the latest data-processing techniques enables passive, real-time monitoring of participants via wearable devices, with automated data cleaning to streamline outcome measurement over time. For example, DHTs can be pre-programmed to match the fields in the electronic clinical report form, enabling direct data transfer without the need for data cleaning and reducing potential transcription errors. AI can also send reminders tailored to individual lifestyles to improve adherence to trial procedures and proactively monitor participants for safety and adverse events (for example, AI can be trained to learn from heart rate, blood pressure, temperature and activity data gathered from wearables to predict future events).[p13] Naturally, the specific method of AI implementation will influence how it is regulated. Good Clinical Practice (GCP) guidelines state that the investigator is responsible for medical decisions during the trial and must have control of, and ongoing access to, the data. If decentralised CTIMP monitoring devices can provide 24/7 data streaming and AI can make decisions autonomously, how can a human or team of humans possibly manage this vast influx of data? Key considerations for future deployment of AI-driven solutions include AI literacy, ethics and the development of data analytics skills among healthcare professionals, patients, researchers and regulators. Implementation science studies involving deployment and validation of AI decision support systems (DSS) in real-world clinical settings and human–AI interaction studies are currently limited in number; but such research holds great promise for unlocking the potential of AI-informed DHTs in CTIMPs.[p14] Open-box AI, which enables observers to understand AI decision-making processes, will be important when integrating AI in CTIMPs, because it restricts data input and decisions to dimensions and timescales manageable by humans and thus is more likely to be accepted by regulatory authorities. Similarly, restrictions must be applied to AI tools that modify their algorithms during processing because a 'moving target' would be very difficult to validate within a CTIMP setting. The level of expertise required to fully realise the benefits of DHTs to collect passive, real-time data in decentralised CTIMPs requires the creation of decentralised trial teams and specialised roles within the pharmaceutical industry to turn these opportunities into tangible benefits. However, several barriers have emerged, which are currently slowing the pace of implementation and, in some cases, have led to a reduction of investment in these opportunities. Therefore, we will next highlight the barriers related to DHT deployment in decentralised CTIMPs.

POST-SCREEN

Barriers to real-time DCT data collection

Regulatory complexity

Successful, passive, real-time data collection in decentralised CTIMPs depends on patients operating the DHT safely and effectively. Because CTIMPs are approved and audited by national regulatory authorities, laws and guidance help ensure the effective use of DHTs in these trials.[p15] DHTs specifically designed for remote data collection can be exempt from registration as a medical device.[p15] However, when not governed by medical device regulations, unsurprisingly, given that DHTs used in decentralised CTIMPs serve a medical purpose and interface with patients, the information needed to support their use mirrors that required for medical device registration. For example, recent FDA guidance suggests that device control, verification and validation, usability, technical performance, labelling and use instructions, elements essential for medical device technical file submissions, should be included in the data package supporting DHT use in a DCT.[p15] However, the decentralised trial guidance documents do not cite international standards that guide the generation of such data, like ISO13485 for device control requirements or IEC62336 for usability engineering.[p16],[p17] This can cause confusion, and some might view the exemption of a DHT from medical device registration in a decentralised CTIMP as a way to reduce costs for remote device implementation. This is a mistake that could result in the remote data collection components of a trial being the reason for regulatory approval rejection. An alternative approach of using established medical devices in decentralised CTIMPs must also be carefully considered, because they must be used within their registered intended purpose.[p18] Therefore, although the device might be capable of measuring the required real-time data passively, without modification to its registered status in a CTIMP, the remote collection and transmission of trial data might exceed its registered purpose and therefore require the generation of additional data to validate the device's use in the CTIMP.[p19]

Further consideration is also necessary if a new device or an existing medical device measures a new clinical endpoint in a decentralised CTIMP, because this new endpoint must be validated before use.[p15] The combined risk of using a new DHT and a new endpoint, each tested in relatively few patients, in a large CTIMP could lead to trial failure despite a strong clinical response to a novel intervention (Figure 1). This high risk

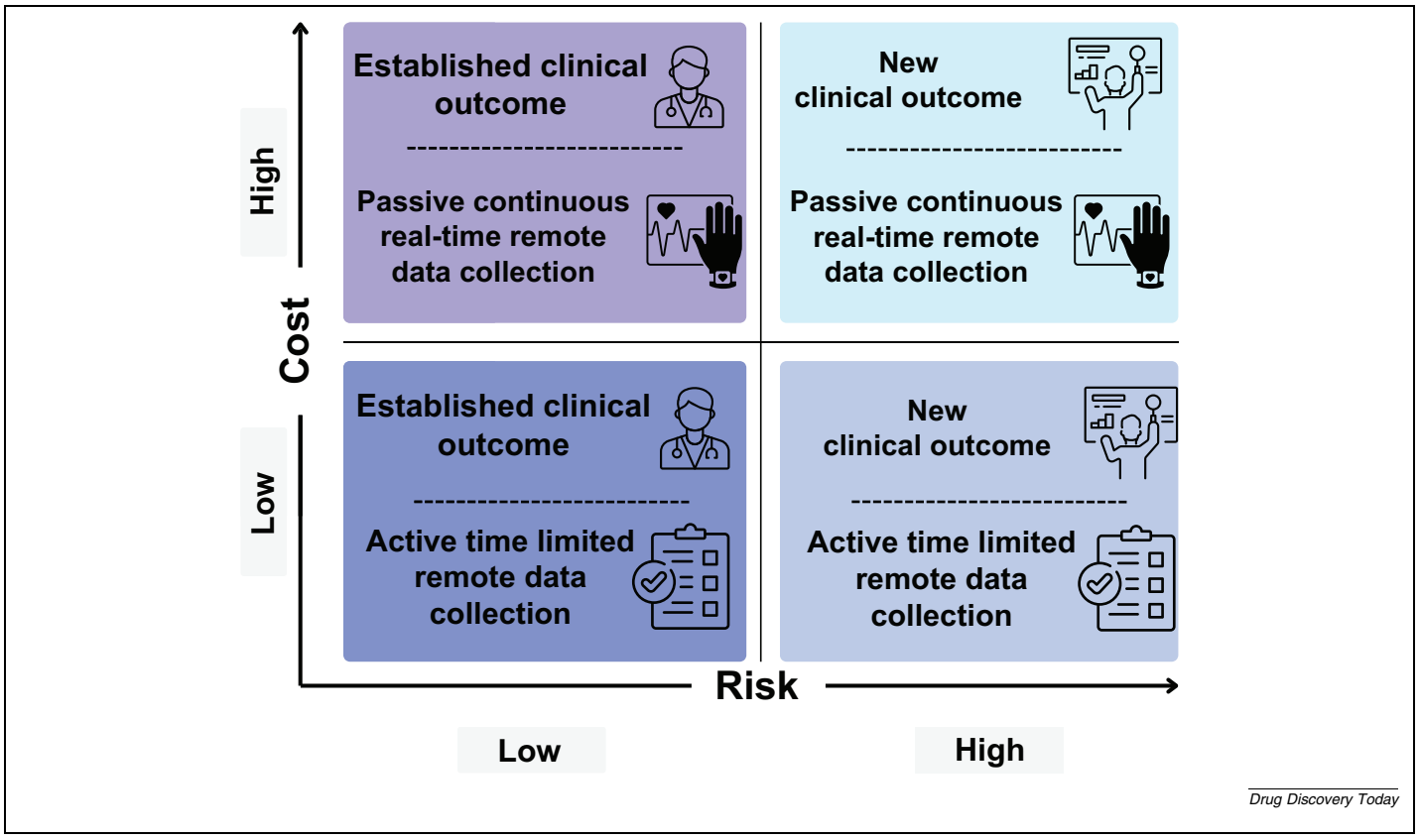

FIGURE 1
Risk–cost matrix for decentralised CTIMP clinical trials.

necessitates a solid justification for implementation, which in turn requires more evidence, especially regarding the patient benefits of decentralising CTIMPs. More evidence would support an accurate risk–benefit analysis of decentralisation of CTIMPs during trial design. Although some in-house models have been developed within large pharmaceutical companies to assist with this process, there remains a need for open-access tools to support consistent decision making across different types of organisations and trial locations.

Patient–device interface

To maximise patient benefits from the decentralisation of CTIMPs, positive patient interactions with deployed DHTs are essential. However, it is unlikely that decentralised trial activities will realise the full potential advantages, such as reducing costs, improving efficiency and increasing the success rate of CTIMPs, simply by providing participants with a mobile phone to document patient-reported outcomes.[(p20)] In fact, the initial focus of DCTs on DHT-recorded patient-reported outcomes has contributed to the scarcity of data demonstrating their impact on trial participants. Available evidence indicates that DCTs can significantly reduce participant screening failures (by ~30%) and protocol amendments (from 3.3 per standard trial to 2.4 per DCT).[(p20)] Reducing screening failures largely results from reaching a more diverse population through remote consent, whereas fewer protocol amendments are mainly due to greater acceptability of trial procedures among participants. Nevertheless, it remains uncertain whether process digitisation, rather than decentralisation per se, is responsible for these changes.[(p21)] We found no objective data to assess the effect of decentralisation on CTIMPs. Likewise, no original research has demonstrated that DCTs reduce the burden of trial participation, improve data objectivity or authenticity, decrease participant dropout or enhance the likelihood of trial success. This partly stems from the limited use of DHTs to collect passive, real-time data, because trials that do not employ these technologies cannot fully realise their potential benefits. The lack of data supporting the advantages of DCTs makes risk–benefit assessment difficult, creating barriers to deploying passive, real-time DHTs in decentralised CTIMPs.

Another barrier to deploying passive, real-time data-collection devices in CTIMPs is trial participant concern that digital technologies are replacing personal contact with clinically trained staff.[(p22)] This concern is expressed through objections to the impersonal nature of electronic informed consent procedures, the potential for delayed responses to adverse events in locations remote from clinical sites, the patient burden of wearing remote data collection devices or using them in daily life, the need for high digital literacy and the risks of data hacking or misuse.[(p23),(p24)] However, passive, real-time monitoring DHTs, designed to address these human factors and concerns, could not only reduce these issues but also improve the patient experience and safety

compared with traditional clinical settings. For example, passive, real-time monitoring of physiological measurements could enable swift responses to adverse effects and prevent their escalation into serious events.[p25] Additionally, passive, real-time collection of digital outcome measures could lessen the frequency of clinical trial site visits and minimise disruption to participants' everyday routines.[p26],[p27] Any worries that passive, real-time monitoring might replace human oversight can be mitigated through participant education. Reassuring participants that trial staff will use alarm systems and standard operating procedures to respond to signals outside acceptable ranges should make it clear that DCTs can provide improved opportunities for 'anomaly detection', data recording and event prediction, thereby enhancing participant safety. These advantages apply equally to CTIMPs and pilot or observational studies. To fully realise these benefits, the safety of participants using DHTs in CTIMPs must be considered during the ethical review process. This involves training ethics committee members to handle the added complexity of DCTs and ensuring transparency in decentralized CTIMP ethical reporting so that safety standards are uniformly upheld across trials. Data must also be gathered and collated on the safety of clinical trials using DHTs.

Economic barriers hinder the large-scale adoption of passive, real-time data-collection technologies in CTIMPs. This affects not only the trial sponsor, who might have to pay for the devices, but also the patients. Some patients might be encouraged to join a trial if they are given a smartwatch. However, others might worry about losing or damaging an expensive, passive, real-time data capture device, which could disrupt their daily routine, compromise data authenticity or increase their stress. Custom applications on trial participant mobile phones have been used to collect patient-reported outcome measures (commonly used during COVID-19) within time-limited, activity-based frameworks in non-CTIMP studies.[p5] This indicates that 'bring your own device' (BYOD) strategies could be an alternative way to implement DHTs in decentralised trials without high cost. In pilot trials or observational studies this approach allows the DCT trial format to be deployed with minimal investment, greatly enhancing its appeal.[p6] This has led to the utilisation of electronic diaries, electronic clinical outcome questionnaires and patient engagement dashboards across various DCTs, with more-adaptable trial formats incorporating more-innovative DHTs (Figure 2). Although a wide range of DHTs is available to record data remotely, from virtual reality (VR) headsets to personal mobile phones, the most innovative tools are often deployed in mechanistic studies, where there are fewer regulatory constraints and endpoints are more exploratory. In CTIMPs, relying on trial participant phones for data collection is unlikely to meet the reliability standards, because it is difficult to verify the accuracy of measurement systems built into or added onto portable mobile phones. Furthermore, mobile phones are unlikely to meet the strict data privacy and security standards of CTIMPs unless each participant has the latest phone model and the systems to lock down phone functions are implemented successfully. Developing bespoke platform technologies that could be reused in multiple, passive, real-time DHTs for

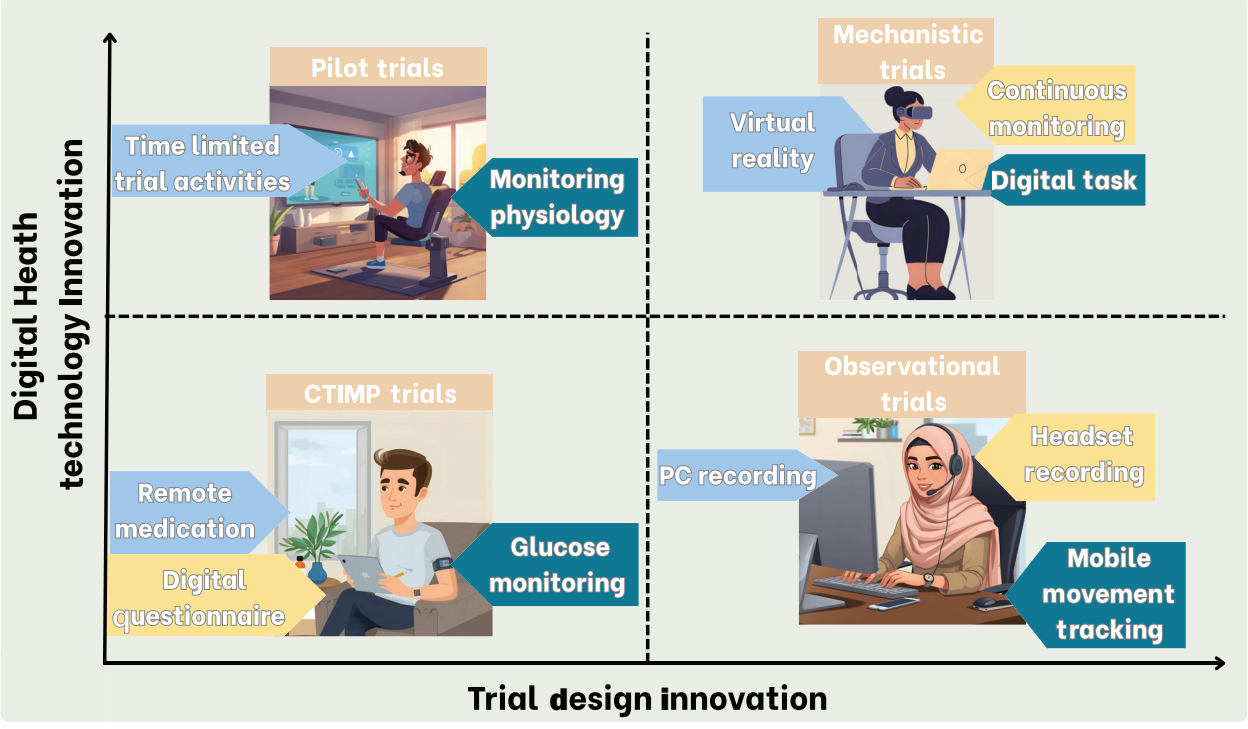

FIGURE 2
Innovation matrix for decentralised clinical trial formats. Cartoons generated using AI.

decentralised CTIMPs is one alternative approach to address the economic challenges. These platform technologies should be simple, small and discreet data-recording devices that can be recharged via a docking station designed for secure data transfer. This strategy could lower the cost of recording devices and reduce the burden on participants when deploying DHTs in decentralised CTIMPs.

Real-time data capture device capability

Passive, real-time data collection in decentralised CTIMPs requires DHTs suited for everyday use. Several available DHTs can collect real-time physiological data, such as heart rate, electrical activity, oxygen saturation and pulse rate, as well as chemical data, such as glucose levels and electrolyte levels. The FDA maintains a database of >250 devices, termed 'sensor-based digital health technology' (sDHT), which could be suitable for inclusion in medical product development programmes. However, most of these devices were not specifically designed for passive, real-time data collection in CTIMPs, and it is often unclear whether they are appropriate for this highly regulated setting. For instance, EpiMonitor and EpiWatch have both been approved by the FDA for passive, real-time detection of epileptic seizures. Nevertheless, although they have been used in several pilot and real-world clinical studies, neither has been employed in CTIMPs.

The reliability of sensors that acquire signals in DHTs is essential for decentralising data collection in CTIMPs. Although electrophysiological sensors that monitor body temperature, tactile pressure sensors capable of measuring physical activities, pressure sensors that assess body weight and optical sensors that determine blood oxygen saturation levels are available, they must be validated for use across a wide range of scenarios if they are to be employed for remote measurements in CTIMPs.[p28],[p29] Consumer products used daily are often not sufficiently precise to be included as measuring devices in a CTIMP. For instance, among 21 different commercial, passive, real-time step counters, significant effects of wear location, walking speed and age on measurement accuracy resulted in a mean percentage error of up to 50%.[p30]

More-specialised recording approaches that measure electrical activity in various body tissues, including neurons and muscles, are also suitable for decentralised CTIMPs. These methods can enable direct communication between the brain and external devices, such as prosthetic limbs or computers (e.g., Synchron Switch or Picostim-DyNeuMo). Standard electrophysiological techniques for brain-controlled devices include electroencephalography (EEG), electrocorticography (ECoG) and implantable electrodes.[p31] These innovative approaches could transform future decentralised CTIMPs by providing real-time monitoring of brain activity, leading to more-accurate and personalised clinical trials. However, to facilitate their development and application, the significant challenges of sensor biocompatibility, invasive device implantation and the lack of sustainable power and secure wireless data transmission must be addressed. Additionally, these DHTs are invasive and are likely to be classified as medical devices when used in CTIMPs. Furthermore, when employing invasive devices, the protection of the rights, safety and well-being of study patients, and the generation of reliable and meaningful results, must be maintained, which requires further research, especially for devices used across diverse study populations.[p32]

An alternative approach for achieving passive, real-time measurement of clinical outcomes using DHTs in CTIMPs is to monitor chemical biomarkers. The sensing electrodes in wearable chemical biomarker devices are typically connected to a transducer, such as a potentiostat, which converts electrochemical measurements into electronic signals that are then transformed into relevant concentrations and displayed on the tethered device or transmitted to a mobile app. Advances in electrochemical sensors, including screen-printed systems, enable highly sensitive and selective measurement of target analytes. Recent 2D materials, such as graphene and MXenes, enable smaller electronics and significantly enhance the dimensions, sensitivity and selectivity of these sensors, offering promise for new device designs tailored for decentralised CTIMPs.[p33] Real-time chemical measurements are currently achievable with continuous glucose monitors (CGMs), which have proven effective in individuals with type 1 diabetes receiving intensive insulin treatment (e.g., Dexcom G7, Signos Glucose Monitoring System). These regulatory-approved devices are validated for supporting clinical decisions and have been deployed in decentralised CTIMPs (Table 1).[p35] CGMs involve placing a sensor beneath the skin and using a patch-style power pack. The data collected from CGMs surpass those obtained through the traditional 'finger-pricking' method for blood glucose measurement. Trials using CGMs have established innovative endpoints for continuous data series that accommodate the size and complexity of the resulting datasets. CGMs have also been used as primary endpoints in CTIMPs, offering an excellent example of how DHTs can enable the decentralisation of CTIMPs. However, impanted GCM are invasive and not ideal. The development of a new non-invasive technology capable of sampling blood glucose over time would be a major advancement. Several devices have been described in the literature but none has yet been employed in DCTs.

The requirement for multiuse DHTs to be deployed in CTIMPs means that continuous chemical monitoring devices should ideally detect multiple analytes to ensure broad applicability and sustainability; but there are no FDA-cleared devices in this category of the sDHT database. This necessitates the extraction of biomarkers from bodily fluids such as blood, saliva or interstitial fluid (ISF). The skin ISF is a rich source of biomarkers, including small molecules and electrolytes, as well as macromolecules such as cytokines and nucleic acids. However, ISF sampling and biomarker analysis in this context are challenging. Whereas microdialysis, suction blister and wick extraction methods are effective, the small volume of ISF samples obtained and the complexity of these techniques make them impractical for DCTs.[p36] Skin stretching, which enlarges the skin appendages, offers a non-invasive and needle-free approach to extracting up to 3 μl of ISF.[p37] Alternatively, suitably engineered microneedle-array patches (MAPs) can be used to extract ISF from the viable layers of the skin in a minimally invasive manner.[p38] Likewise, applying electrical currents to the skin can extract analytes from the tissue and provide real-time chemical measurements.[p39] Nevertheless, skin stretching, MAPs and electrical-current-based devices remain under development, and their commercialisa-

TABLE 1

Examples of published, peer-reviewed, interventional decentralised clinical trials using real-time data monitoring systems.

Intervention	Condition	Decentralised elements	Impact	Refs
Insulin Glargine 300 U/ml vs Insulin Degludec 100 U/ml	Type 1 diabetes	Remote continuous glucose monitoring using an implanted device	Time in glucose range was similar in the two insulin treatments groups (52.4 ± 14.0 vs 0.49.3 ± 13.9% Gla-300/IDeg-100, respectively)	(p54)
Pulsed inhaled nitric oxide	Fibrotic interstitial lung disease	Physical activity as measured by actigraphy via a wearable device. Patient-reported outcomes using the University of California San Diego shortness of breath questionnaire and the St George's Respiratory Questionnaire (SGRQ)	A placebo-corrected clinical benefit of 12.3 min/d increase in sustaining moderate to vigorous physical activity was observed in the treatment group. Clinically meaningful beneficial trends were observed for the University of California San Diego shortness of breath questionnaire (6.05 points) and the SGRQ total scores (3.75), as well as the SGRQ activity (5.84) and SGRQ impact (6.30)	(p55)
Canagliflozin	Heart failure	Completely decentralised with no face-to-face visits. Electronic informed consent, direct home delivery of study medication, completion of the primary endpoint by a mobile application and a Fitbit Versa 2 (San Francisco, CA) to monitor activity	The 12-week change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score was 4.3 points [95% confidence interval (95% CI): 0.8–7.8; $P = 0.016$] higher with canagliflozin than with placebo, meeting the primary endpoint (no conclusions were made on Fitbit-measured activity)	(p56)
Prasinezumab	Parkinson's disease	Exploratory endpoints of video-based ratings and assessments of motor function and activity from a smartphone and smartwatch application	Prasinezumab therapy had no meaningful effect on global or imaging measures of Parkinson's disease progression as compared with placebo. There was no significant effects of treatment on any exploratory endpoints	(p57)
Tirzepatide	Type 2 diabetes	Time that continuous monitoring glucose values were in the tight target range (71–140 mg/dl)	Patients given once-weekly tirzepatide (pooled 10 mg and 15 mg groups) had a greater proportion of time in tight target range compared with patients given insulin degludec [estimated treatment difference 25% (95% CI 16–33); $P < 0.0001$]	(p34)
Asthma therapy	Severe asthma	Digital inhaler adherence, digital peak expiratory flow (ePEF), patient-reported asthma control and exacerbation history	In the intention-to-treat analysis at week 32, 14 (14%) active and 31 (32%) control patients had a net increase in treatment compared with baseline [odds ratio (OR) 0.31 (95% CI 0.15–0.64), $P = 0.0015$]	(p58)
Standard heart failure therapies	Chronic heart failure	Implanted device to monitor pulmonary arterial pressure	The difference in mean change in Kansas City Cardiomyopathy Questionnaire overall summary score at 12 months was 7.13 (95% CI 1.51–12.75; $P = 0.013$) between groups (+7.05 in the CardioMEMS group, $P = 0{\cdot}0014$ and −0.08 in the standard care group, $P = 0.97$)	(p59)

tion, validation and deployment at scale in CTIMPs remain objectives for the future.

One important factor in assessing the suitability of a DHT for use in CTIMPs is its sustainability. Because the healthcare industry is among the highest carbon-emitting sectors in the industrialised world, there is an increasing focus on environmental sustainability.(p40) This imperative can be seen as a barrier and an opportunity for decentralised CTIMPs, depending on their design. The recently released White Paper from the Health Systems Task Force of the Sustainable Market Initiative (2022) estimated that the global clinical trial footprint each year results in ~100 million tonnes of greenhouse gas emissions.(p41) However, there are limited data available on how decentralised CTIMPs will affect this carbon footprint. It could be argued that fewer patient visits might improve trial sustainability by lowering CO_2 emissions, and digital data collection certainly could reduce paper use; nevertheless, there is a risk that single-use DHTs could negate these benefits. Ongoing research, including efforts by the Sustainable Healthcare Coalition and the Pistoia Alliance, aims to thoroughly understand the clinical research process. A key objective is to quantify trial-related emissions from DCTs using innovative DHTs, which could guide future design of collection devices. Sustainability considerations in decentralised CTIMPs should foster the development of core clinical monitoring device platform technologies that are cost-effective to deploy and reuse. Such approaches must be encouraged and supported through effective collaboration among stakeholders involved in DCTs. If successful, this could enable trials to transition from a focus on clinical units to patient homes.

Trials at home

Using mobile health apps, wearable devices, point-of-diagnosis testing devices and telemedicine platform solutions should enable a participant's home, a place of comfort and security, to serve as a site for a clinical trial rather than the hospital ward (Figure 3).(p20),(p42) Utilizing the home as a remote clinical trial site appears feasible, because trial participants increasingly seem capable of adopting DHTs outside the clinical setting when issues

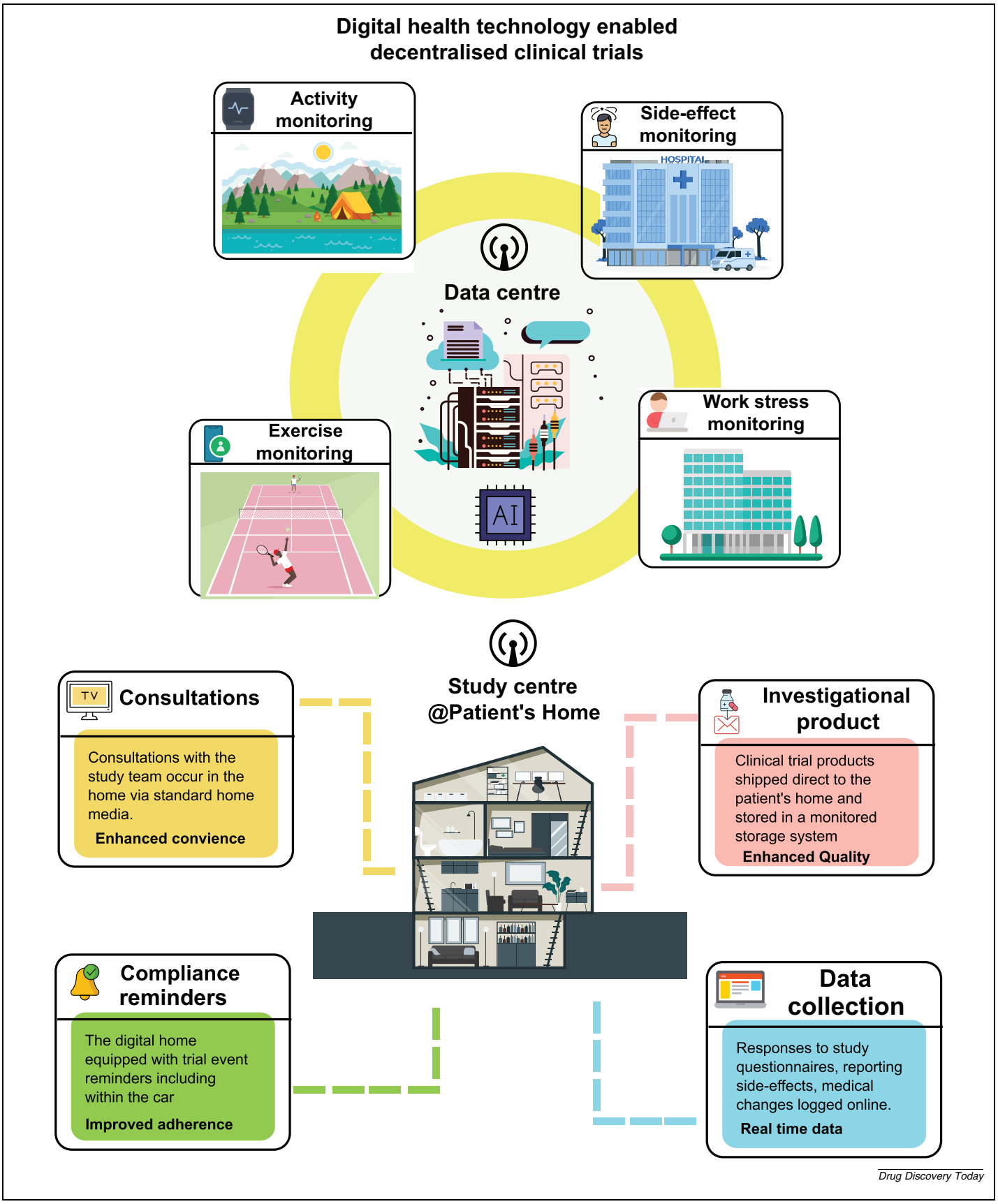

FIGURE 3
Schematic demonstrating patient home-focused decentralised trials.

at the device–patient interface are addressed. Engagement with electronic diaries, electronic clinical outcome assessments, patient engagement dashboards, digitally enabled recruitment and digital enrolment has contributed to a general increase in DHT use in clinical trials (from <1% in 2010 to >10% in 2020).[(p43)] However, the absence of passive, real-time monitoring in DCTs means that decentralising many trial activities into participant homes has yet to be fully realised. In 2021, a systematic review reported that none of the 30 completed DCT trials utilised passive, real-time monitoring DHTs for data collection in participant homes.[(p5)] A more recent literature review by the authors, focusing on large prospective DCTs, identified only seven trials employing DHTs for real-time data collection; four were CTIMPs, with just two employing passive, real-time data collection for primary endpoints (Table 1). The two CTIMP trials utilising passive data collection described in Table 1 used CGMs, which are already registered as medical devices. This does not mean that DHTs have not been used to collect real-time data in DCTs – several pilot studies have illustrated the potential of real-time measurements at patient homes.[(p43)] For example, smartwatches and phones have been used in MS to measure physical activity through passive and active tests.[(p8)] In Parkinson's disease several commercially available technologies monitor movement to quantify motor symptoms and assess activity. Nevertheless, these technologies have not yet been employed in CTIMPs. Theoretically, these devices could be used in decentralised CTIMPs but they must be validated for data collection according to regulatory guidance. A three-stage validation process has been established, comprising verification, analytical validation and clinical validation.[(p44)] Although this process adds an extra burden for investigators, it might not be prohibitive in the context of a costly Phase III clinical trial, depending on the scope of the clinical validation phase – for instance, measuring a traditional clinical endpoint remotely can be simpler than validating a device for novel digital endpoints. For example, Fortin et al. (2021) described the validation of a new continuous blood-pressure monitoring device in a relatively straightforward study assessing the effectiveness of a new antihypertensive drug.[(p45)] Conversely, the DHT used to measure cognitive and motor tests in the Parkinson's trial mentioned by Adams (2020) would be considered a novel biomarker, requiring more-extensive and costly validation following the BEST Guidelines or similar standards.[(p46)]

Scaling the use of a new DHT from a pilot study to a large decentralised CTIMP must also consider data security, especially when the primary data collection site is the patient's home. Trial data need to be generated within a traditional trial ecosystem (trial management systems, quality assurance systems, trial master file systems, etc.), which clinical research professionals oversee.[(p47),(p48)] Data quality is just as important and requires fully integrated systems that improve data management and reduce processing risks. This is particularly challenging for BYOD approaches. Passive, real-time data collection will produce large datasets, requiring extensive processing and storage systems to maintain the integrity of information collected 24/7 from multiple sensors per participant. Communication from each sensor must comply with existing data and healthcare regulatory standards, including the EU General Data Protection Regulation (GDPR), UK Data Protection Act (DPA) 2018 and US National Institute of Standards and Technology (NIST), which mandate that users give informed consent for data collection, processing, storage and sharing with authorised parties.[(p49),(p50)] This can be achieved through appropriate privacy consent, usually collected alongside participation consent, which must be considered in the CTIMP DCT design.

Future directions

As the global population increasingly uses digital technology in daily life, CTIMPs must adopt and benefit from these advances. However, to do so, barriers to passive, real-time monitoring by DHTs in decentralised CTIMPs need to be removed, enabling the realisation of trial decentralisation benefits. The regulatory complexity of integrating DHTs into CTIMPs could be addressed through a customised fast-track regulatory pathway, new guidance, specialist workshops and support for developing new DHTs specifically for decentralised trials. While the use of medical devices in CTIMPS should remain an option, incentives for creating bespoke technologies are essential to stimulate interest and highlight their potential profitability.

Developing new DHTs tailored for decentralised CTIMPs would also resolve issues related to the patient–device interface, provided that the trial context and human factors are incorporated into the design plans. This involves aligning regulatory guidance with existing medical device procedures, which already account for human factors and other design considerations. Although these new devices could enhance current data recording technologies in decentralised CTIMPs, designing a series of sensors without considering data transfer compatibility would be inefficient. An effective solution would be to implement a plug-and-play home 'base station', similar to a Wi-Fi router, with universal features, combined with custom sensors for ongoing trials. This setup could reduce barriers to implementing decentralised CTIMPs and address sustainability issues but would require a coordinated effort among stakeholders. Initiatives such as the NIHR Remote Methods of Trial Delivery project in the UK, the Trials at Home project funded by the EU and the DCT & Research Alliance in the USA have laid a strong foundation for advancing decentralised trial principles and practices.[(p51),(p52),(p53)] However, greater focus on the specific needs of CTIMPs and on passive, real-time data collection is essential to fully unlock the advantages of this transformative approach to clinical studies.

Concluding remarks

DCTs could significantly shape the current landscape of clinical assessment. However, major barriers to the successful decentralisation of CTIMPs remain, including regulatory complexity, the patient–device interface, device capability to capture real-time data and the feasibility of conducting trials at home. These challenges are not insurmountable but they probably cannot be overcome by individual trial groups. Stakeholders involved in clinical trials are encouraged to develop coordinated initiatives to establish standards and working procedures to decentralise CTIMPs. This must be achieved through multidisciplinary teams to ensure all factors influencing the implementation of CTIMPs are considered. Tools and guidance are needed to: better (i) assess the risks

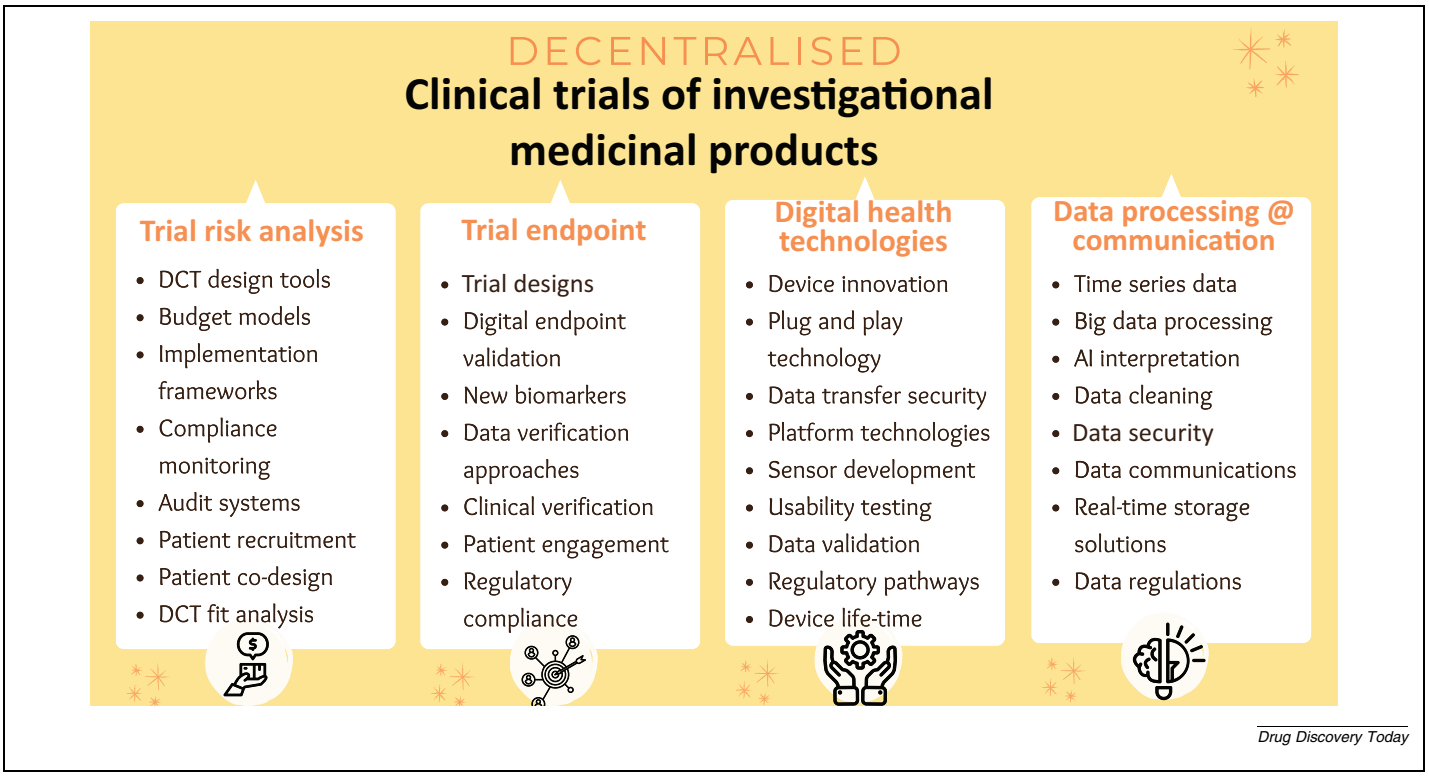

FIGURE 4

A schematic detailing the collaborative future that decentralised CTIMP work should focus on.

of decentralisation; (ii) develop new endpoints or adapt existing ones to facilitate decentralisation; (iii) verify the suitability of DHTs for use in CTIMPs; and (iv) evaluate the appropriateness of data communication and processing workflows (Figure 4). This guidance should then be used to inform regulatory frameworks governing decentralised CTIMPs to create meaningful impact. Such an approach will promote the adoption of the DCT format in regulatory studies assessing new medicinal products, benefiting drug developers and patients alike.

AI use

AI was used to generate the cartoons in Figure 2.

Competing interests

Authors declare that they have no competing interests except CC has received advisory, consulting or lecture fees from AbbVie, Astex Pharmaceuticals, Bial, Britannia, inMuneBio, GSK, Mission Therapeutics, Merz and Roche. SP is a director and shareholder of PM Life Sciences, which works with Life Science organisations involved in decentralized trials and digital health technologies.

CRediT authorship contribution statement

Abdel Douiri: Writing – original draft. **Mohamed A. Alhnan:** Writing – original draft. **Muhammad Rizwan Asghar:** Writing – original draft. **Konstantinos Balaskas:** Writing – original draft. **Faiza Benaouda:** Writing – original draft. **John Bolodeoku:** Writing – original draft. **Clare Campbell-Cooper:** Writing – original draft. **Camille Carroll:** Writing – original draft. **Tao Chen:** Writing – original draft. **Keith Dorricott:** Writing – original draft. **Thierry Escudier:** Writing – original draft. **Carsten Flohr:** Writing – original draft. **Ben Forbes:** Writing – review & editing, Writing – original draft. **Richard H. Guy:** Writing – original draft. **Stephanie Langouet:** Writing – original draft. **Anthony Lockett:** Writing – original draft. **Rayka Malek:** Writing – original draft. **Angela May:** Writing – original draft. **Graham R. McClelland:** Writing – review & editing, Writing – original draft. **Sara M. Nasereddin:** Writing – original draft. **Alejandro J. Paredes:** Writing – original draft. **Sheuli Porkess:** Writing – original draft. **Eddie G.M. Power:** Writing – original draft. **Richard E.K. Russell:** Writing – original draft. **Richard Stephens:** Writing – original draft. **Heba Sailem:** Writing – original draft. **Daniel Sebastia-Saez:** Writing – original draft. **Matthew R. Sydes:** Writing – original draft, Conceptualization. **John Weinman:** Writing – original draft, Conceptualization. **Yunlong Zhao:** Writing – original draft. **Stuart A. Jones:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization.

Funding

Wellcome Career Development Award (HS), MRC (MC_UU_00004/08) (MS), EPSRC EP/X013294/1, EPSRC EP/S021159/1(TC), Royal Society, Applied Microbiology International and EPSRC (AP), Edmond J Safra Foundation, Parkinson's UK, NIHR, Cure Parkinson's (CC), King's Health Partners/Guy's

and St Thomas Charity 'MLTC Challenge Fund' (award reference: EIC180702) (AD), EPSRC EP/S021167/1 (SAJ and FB).

Data availability

All information is available.

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