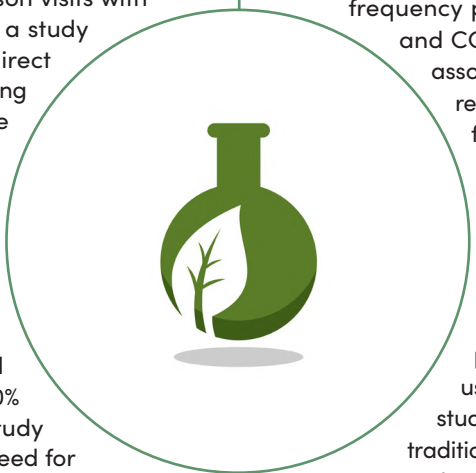
Study Designs and Digital Technologies for Sustainable Clinical Trials

The clinical trial industry is essential for ensuring the safety and efficacy of new medicines; however, it is also a significant contributor of greenhouse gas emissions. The Sustainable Healthcare Coalition estimates clinical trials may be responsible for up to 100 megatons of CO_2 emissions annually, about the same emissions produced by a country the size of Belgium.[1] The main sources of these emissions are thought to include trial-related travel by study participants and site staff, deliveries of trial equipment and energy usage by clinical study sites.[2] Given the clear role of CO_2 emissions in climate change, the clinical trial industry must adopt new solutions to improve the sustainability, while enhancing patient access and retention as well as the patient experience. Those solutions that are showing promise include patient-centric study designs, virtual clinical studies, adaptive study designs, electronic patient-reported outcomes (ePRO) and the use of digital technologies.

Patient-Centric Study Designs

Patient-centric study designs consider a patient's needs and preferences with the aim of reducing the burden on study participants. Those patient-centric approaches that may impact trial sustainability include the use of shorter trial durations and reductions in the frequency and number of required clinic visits e.g., using remote monitoring technologies or telemedicine. An example of a patient-centric study design can be seen in the CHIEF-HF trial, which aimed to evaluate whether the SGLT2 inhibitor, canagliflozin significantly reduces symptom burden in patients with heart failure.[3] This trial was designed to reduce the need for in-person visits with direct engagement of patients through a study website, electronic informed consent, direct home delivery of study medication, reporting of the primary endpoint by a mobile application, and use of a Fitbit to monitor activity.[3] Patient-centric approaches can make trials more convenient for patients through fewer patient journeys, which in turn can lower fuel consumption and help reduce CO_2 emissions. The involvement of patients in the design of clinical trials can also benefit patient recruitment and retention. It is estimated that more than 80% of clinical studies face problems with study recruitment resulting in delays and the need for additional study sites.[4] Furthermore, almost a quarter of participants involved in cardiovascular clinical studies drop out before completion.[5] Through improved recruitment and retention, patient-centric approaches can help reduce the number of participants required to meet the study outcomes and the resources needed to complete the study.



Decentralised Clinical Trials

Decentralised clinical trials (DCTs) describe trials where some of the trial activities take place at sites other than the clinical investigation site, such as the patient's home or a local clinic. DCTs often involve the use of digital tools and platforms to facilitate communication between research teams and study participants. A notable example includes the DeTAP study – a trial, involving the physiologic monitoring of patients with atrial fibrillation receiving oral anticoagulation therapy.[6] The DeTAP study utilised telemedicine, eConsent, remote monitoring devices, and ePROs collected via a mobile application to fully decentralise research activities.[6] DCTs can improve trial sustainability by reducing the distance or frequency participants travel to clinical study sites and CO_2 emissions. The improved accessibility associated with DCTs can help speed up study recruitment, reducing timelines and the need for additional study sites. DCTs can also lead to the more efficient use of energy resources through reduced reliance on physical study sites and the generation and handling of study-related paperwork. However, the manufacture, distribution and use of digital tools and data storage platforms can also contribute to energy usage and CO_2 emissions. Nonetheless, one study estimated that the full digitalisation of a traditional clinical study could lead to a more than 90% reduction in energy usage.[7]

Adaptive Study Designs

Adaptive study designs allow for the modification of an ongoing clinical trial design based on evidence accumulated during the study. This is in contrast with traditional clinical studies, where the study design is fixed at the outset and does not change during the course of the study. These modifications may include refinement of sample sizes, targeting specific

patient subpopulations, treatment or dosage regimens, study endpoints and trial duration. Adaptive trial designs have been utilised in cardiovascular studies such as the ANTHEM-HFrEF, a study evaluating the impact of autonomic regulation therapy in heart failure patients, which employed a Bayesian approach for sample size selection.[8] Adaptive study designs can help improve trial sustainability by reducing participant numbers and study timelines, potentially reducing the resources needed to complete the study. The optimisation of clinical trial designs can also help increase the likelihood that the study will meet its endpoints, saving the time and resources spent on failed studies.

Electronic Patient-reported Outcomes

ePROs are health outcomes directly reported by patients by means of electronic devices such as smartphones, tablets or web applications. ePROs are commonly used in clinical trials to provide information about a participant's symptoms, daily functioning, quality of life and response to therapy. Notably, more than a quarter of the clinical trials currently being conducted are thought to involve ePROs.[9] The CHIEF-HF study is one such study, where the outcomes were assessed using an app version of the Kansas City Cardiomyopathy Questionnaire for quantification of symptom frequency and severity, and Fitbit monitoring of daily step counts.[3] ePROs can enhance study data quality by enabling more frequent and real-time reporting of a study participant's health status. ePROs can contribute specifically to trial sustainability by reducing the number of appointments participants need to attend, thereby reducing required clinic time and trial-related travel and its environmental impacts. Additionally, the incorporation of ePROs into study designs can conserve resources by reducing study-related paperwork and the associated administrative burdens.

Digital Technologies

Digital technologies are increasingly being used to enhance data quality within the clinical trial setting by enabling the continuous and remote collection of health data from study participants during their everyday activities. These digital technologies range widely and may include software (e.g., smartphone apps), and hardware (e.g., wearables) solutions. The number of clinical trials incorporating digital technology was estimated at 11% in 2020 and is projected to reach 70% by 2025.[10] One example is the LINK-HF study, which utilised a multisensor disposable patch to continuously monitor a range of physiological parameters and detect oncoming heart failure exacerbations.[11] Another recent example, the eBRAVE study, utilised a smartphone app to screen for pulse wave irregularities and detect atrial fibrillation in individuals at risk of stroke.[12] Digital technologies can contribute to trial sustainability by reducing the need for participants to travel to study sites to have measurements performed and conserving energy associated with study site operations. Additionally, digital tools can provide more accurate and real-world data as well as additional data points, helping to reduce the likelihood that the study will need to be extended or repeated.

Sustainable Solutions Driving Clinical Trials

New solutions are crucial for improving the sustainability of the clinical trial industry and reducing its contribution to climate change. The main contributing factor is CO_2 emissions, resulting from trial-related travel and energy usage by clinical study sites. Those solutions showing promise in this regard revolve around adjustments in study designs or the incorporation of digital technologies. These solutions can also improve recruitment and retention by enhancing the clinical trial experience for study participants. However, several barriers exist to their adoption, including concerns over data security and privacy, data quality, participant safety in the absence of physical visits, and accessibility for those with poor computer literacy. Addressing these concerns will not only help minimise the environmental impact of the industry but also help ensure the continued development of new medicines.

REFERENCES

1. https://shcoalition.org/clinical-trials/, visited on 9 October 2024.
2. Sustainable Trials Study Group. Towards sustainable clinical trials. BMJ. 334(7595), 671–673 (2007).
3. Spertus, J.A., Birmingham, M.C., Nassif, M., *et al.* The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. Nat. Med. 28(4), 809–813 (2022).
4. Desai, M. Recruitment and retention of participants in clinical studies: Critical issues and challenges. Perspect. Clin. Res. 11(2), 51 (2020).
5. Hutchison, E., Zhang, Y., Nampally, S., *et al.* Modeling Clinical Trial Attrition Using Machine Intelligence: A driver analytics case study using 1,325 trials representing one million patients. medRxiv. 2021.11.12.21266277 (2021).
6. Sarraju, A., Seninger, C., Parameswaran, V., *et al.* Pandemic-proof recruitment and engagement in a fully decentralized trial in atrial fibrillation patients (DeTAP). NPJ Digit. Med. 5(1), 80 (2022).
7. Kohl, S.H., Schmidt-Lucke, C. Clinical trials to go green–A sustainable argument for decentralised digital clinical trials. PLOS Digit. Health. 2(10), e0000366 (2023).
8. Konstam, M.A., Udelson, J.E., Butler, J., *et al.* Impact of Autonomic Regulation Therapy in Patients with Heart Failure. Circ. Heart Fail. 12(11) (2019).
9. Vodicka, E., Kim, K., Devine, E.B., *et al.* Inclusion of patient-reported outcome measures in registered clinical trials: Evidence from ClinicalTrials.gov (2007–2013). Contemp. Clin. Trials. 43, 1–9 (2015).
10. Chandrasekaran, R., Katthula, V., Moustakas, E. Patterns of Use and Key Predictors for the Use of Wearable Health Care Devices by US Adults: Insights from a National Survey. J. Med. Internet Res. 22(10), e22443 (2020).
11. Stehlik, J., Schmalfuss, C., Bozkurt, B., *et al.* Continuous Wearable Monitoring Analytics Predict Heart Failure Hospitalization. Circ. Heart Fail. 13(3) (2020).
12. Rizas, K.D., Freyer, L., Sappler, N., *et al.* Smartphone-based screening for atrial fibrillation: a pragmatic randomized clinical trial. Nat. Med. 28(9), 1823–1830 (2022).

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