

a key target which the sustainability strategies should focus on (1–4).

Recent estimates further illuminate the magnitude of this challenge. If the „mortality cost of carbon“ metric shows that 4,434 metric tons of CO<sub>2</sub> lead to one excess death, current healthcare emissions could be associated with approximately 550,000 excess deaths (5). For Europe alone, Chen-Xu et al. estimated that healthcare-related emissions would result in approximately 365,047 DALYs and 25.6 billion euros in healthcare costs, assuming that no significant changes occur and based on current underlying expectations (4). In addition, projections suggest that without immediate and coordinated action at the systemic level, the healthcare sector's carbon footprint could triple by 2050 (6). In light of these trends, transitioning toward and investing in sustainable and climate-resilient healthcare thus seems necessary because such investments would eliminate or at least reduce the expenditures to address the consequences. Steps towards sustainable healthcare are therefore inevitable.

### Support in developing sustainable healthcare and “green” trials

One of the strategic frameworks guiding this change is the Net Zero Initiative. Under this commitment, the participants pledged to reduce their emissions by 45% by 2030 and reach net zero by 2050. The concept of net zero denotes a state in which residual anthropogenic emissions should be minimized to levels that can be absorbed by nature. Thereby no added CO<sub>2</sub> will accumulate in the atmosphere and keep global warming to no more than 1.5 °C (corresponds to the pre-industrial level); all in accordance with the Paris Agreement. As of now, 139 out of 199 countries have formally joined the net zero programme (7, 8).

Parallel to the above-mentioned policy commitment, a number of initiatives aimed at accelerating sustainability within healthcare are currently being established. Within the EU, the primary driver supporting environmentally conscious research is Horizon Europe. Horizon Europe programme (2021–2027), encompassing both the preceding and forthcoming programmes, financially supports climate-neutral research and innovation.

Specifically, the following three projects are centred on the development of carbon-neutral and sustainable healthcare systems: *Caring Nature*, *KitNewCare*, and *NetZeroAICT* (9, 10).

The *Caring Nature* project focuses on developing ten innovative solutions aiming to reduce non-supply chain greenhouse gas emissions in the healthcare sector, such as optimized heating, ventilation, air-conditioning and electricity systems, expanded telemedicine, and reduced medical waste. Eleven EU countries, but not Czechia, are participating in this project (11). The *KitNewCare* project is focused on more sustainable kidney care (12). *NetZeroAICT* applies artificial intelligence to computed tomography with digital contrast, which enables to limit contrast media administration to patients (13). In addition, Horizon Europe supports five “green pharmaceutical” projects, aimed at developing innovative sustainable pharmaceutical manufacturing processes, with total funds of 35 million euros (9).

Although none of the initiatives or projects directly targets sustainability in clinical research, it can be assumed that changes from sustainable clinical practice will influence research processes, too, given the interdependence between healthcare delivery and clinical research. Advances in one domain can be expected to propagate into the other, facilitating broader transformation toward environmentally responsible healthcare.

### Sustainability in clinical trials

Clinical trials represent a complex, resource-intensive component of healthcare and clinical research. Their environmental impact has only recently begun to be systematically examined. Specifically, next year marks 20 years since one of the first analyses of the carbon footprint of clinical trials was published. The *Sustainable Trials Study Group* highlighted early that clinical trials contribute substantially to greenhouse gas emissions and emphasized the need for simpler and more efficient trial designs and processes (14). More recently, according to *Sustainable Healthcare Coalition*, an average clinical trial that is registered on [clinicaltrials.gov](https://clinicaltrials.gov) may generate 27.5 million tons of CO<sub>2</sub> emissions, with an estimated total

annual emission from all active trials reaching as much as 100 million tons (15, 16). These findings, though still estimates, underscore the urgency of incorporating sustainability principles into trial methodology.

### How to define a “green” clinical trial?

Even though no universally accepted definition of a sustainable or “green” clinical trial exists, it can be basically characterized as a clinical trial that systematically minimizes or at least considers environmental harms in each phase of its design and execution while ensuring participants' safety and scientific data integrity. Given the substantial heterogeneity among clinical trials, there are currently no established emission thresholds set on average appropriate/ideal emissions, or total or percentages of emission reduction. The current efforts thus focus on evaluating various mitigation strategies to determine the most effective interventions yielding the lowest possible carbon footprint while maintaining operational feasibility.

### Important steps in development of “green” clinical trial, digitization and decentralization of clinical trials

The prerequisite for effective carbon footprint reduction is, first and foremost, the measurement of emissions. Quantitative data allow researchers to identify preferential and high-impact areas, and to prioritize evidence-based mitigation strategies. Energy consumption in research facilities, travelling and distribution, and inefficiencies in protocol design (that can, for example, increase staffing needs) were expected to be the most significant contributors and should thus play a key role in the strategies of reducing CO<sub>2</sub> emissions. This was confirmed by the *Sustainable Trials Study Group* (14). To support emission estimation, the National Institute for Health and Care Research (NIHR), in cooperation with the *Industry Low-Carbon Clinical Trials* (iLCCCT) consortium, has developed and published a carbon calculator – available on the website <https://clinicaltrialcarbon.org/> (17–19). The calculator provides approximate assessments of the carbon footprint based on the trial design. While the calculator captures carbon output,