Clinical trials and environmental sustainability

Review of key considerations to develop climate change mitigation and adaptation strategies

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ISBN 978-92-4-012010-5 (electronic version)
ISBN 978-92-4-012011-2 (print version)

Suggested citation. Clinical trials and environmental sustainability: review of key considerations to develop climate change mitigation and adaptation strategies. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

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Acknowledgements

This publication was developed under the direction and coordination of Katherine Littler (Co-Head of the Health Ethics and Governance Unit, Department of Research for Health), under the overall guidance of Meg Doherty (Director, Department of Research for Health) and Sylvie Briand (Chief Scientist) at World Health Organization (WHO) headquarters. The lead writers were Gabrielle Samuel and Matthew Graham (King's College, United Kingdom of Great Britain and Northern Ireland).

WHO wishes to thank the following individuals for their contributions to the development of this publication.

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- Renata Eloah de Lucena Ferretti-Rebustini, University of São Paulo School of Nursing, São Paulo - Brazil
- Lisa Fox, Institute of Cancer Research – Clinical Trials and Statistics Unit, United Kingdom and MRC-NIHR Greener Trials Group
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- Jean-Marc Hoffmann, University Hospital Zurich, Switzerland
- Jim Huggett, National Measurement Laboratory at LGC, United Kingdom
- Myriam R Laconi, Director, Laboratory of Ovarian Pathophysiology, IMBECU-CONICET (National Scientific and Technical Research Council), Mendoza, Argentina.
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- Laura Richert, University of Bordeaux, France
- Prasansa Subba, University of Copenhagen, Denmark
- Matimba Swana, University of Bristol, United Kingdom
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Executive summary

Clinical trials are critical for the evaluation of the safety, efficacy and effectiveness of interventions designed to improve health outcomes. Trials are also associated with the generation of greenhouse gas emissions (also called carbon dioxide emission equivalents). Approximately 76 000 new trials were registered on The World Health Organizaion's International Clinical Trials Registry Platform in 2023, each producing an estimated 80–2000 tonnes of emissions. Even at the lower end of the estimates, these numbers are significant: 80 tonnes is equivalent to driving a car 12 times around the planet. Depending on the trial, clinical trials are also associated with other environmental harms, including the production of hazardous and non-hazardous waste materials – such as those from pharmaceuticals, air pollution due to road travel and water use.

Given these environmental burdens, it has been argued that there is a moral obligation to reduce the environmental harms associated with clinical trials (in a way that does not compromise the trial's integrity). To ensure that such reductions do not compound existing social inequities in the clinical trial landscape, trials need to be designed and implemented with environmental and social justice in mind. They should adopt methodologies that have a low environmental burden, and ensure proper disposal and treatment of waste to mitigate ecological harm, while ensuring that these processes do not lead to (further) social inequities, specifically but not only in low- and middle-income countries (LMICs). By integrating these practices, the clinical trial research community can continue to advance health outcomes while minimizing environmental harms.

Work is increasingly being done to quantify and, in turn, mitigate environmental harms associated with clinical trials, although these studies have almost exclusively focused on the generation of greenhouse gas emissions. To date, most reports are from a few high-income countries (HICs), with little published data on how emissions and other environmental harms manifest in different global contexts – particularly in LMICs.

Beyond mitigation, minimal attention (in both HICs and LMICs) has been paid to the capacity of clinical trial systems to anticipate, respond to, cope with, recover from and adapt to climate-related shocks and stress (clinical trial climate resilience). There has been, however, been an increasing interest in the effects of changing climates on health care in general and, more specifically, in the resilience of health-care facilities. This will be relevant to trial resilience, given the role many health-care facilities play in hosting clinical trial sites. As the climate changes, clinical trials are likely to become increasingly vulnerable to disruption – for example, from increased flooding, heatwaves and/or other weather events. This can preclude access to trial research site facilities and/or disrupt cold chains or other forms of delivery of biological samples, drugs and medications. Such vulnerabilities are likely to be particularly relevant to clinical trial sites in LMICs – countries that, while disproportionately exposed to the effects of climate change, and while having fewer resources to protect against them, have contributed little to historic global emissions. (They are also relevant to underserved areas of upper-middle-income countries and HICs.)

> To mitigate clinical trial-associated climate harms in a way that is just, a comprehensive approach that places environmental and social justice at the centre of trial development is required

This publication reports on a WHO-commissioned project to identify key considerations for clinical trial climate change mitigation and adaptation strategies that are socially just, and do not compromise the integrity of a trial, with a particular focus on the needs and capabilities of LMICs. In particular, the scope of the report was to review how climate mitigation and adaptation considerations can be included in clinical trial design and practice. The report excludes environmental harms associated with the manufacture and use of interventions being trialled (pharmaceuticals, digital and/or other interventions). It does, however, consider environmental harms associated with the shipping and disposal of these products. Furthermore, to avoid being carbon-centric, it also discusses other environmental harms including plastic, digital hardware and other waste; land and water use; eco and land toxicity; and particulate emissions.

This report should be read in conjunction with other key WHO documentation and guidelines associated with low-carbon, resilient health-care systems, including sustainable procurement. It was produced using a collaborative, iterative and co-produced methodology, including contributors from a range of countries, with a focus on ensuring strong representation from those living and working in LMICs. The study team spoke to 27 clinical trial actors about their perceptions, attitudes and experiences of the opportunities and barriers associated with mitigating the climate and other environmental harms associated with clinical trials, and the climate resilience of clinical trial systems (including 15 from LMICs and 24 with experience of working in LMICs). The findings were compiled with an extensive literature review. The study team developed draft from the initial respondents and other clinical trial actors identified through known networks. All individuals involved in one or more of the processes were invited to be named contributors, although not all accepted.

The report highlights that to mitigate clinical trial-associated climate (and other environmental) harms in a way that is just, a comprehensive approach that places environmental and social justice at the centre of trial development is required. This applies equally to the implementation of trial adaptation strategies. The study team mapped key elements to consider to achieve this, underpinned by the following principles/assumptions.

a. The consideration of environmental harms should be implicit to trial design: good-quality and well-planned trials based on rigorous methodologies are the most effective approach to ensuring that trials are environmentally sustainable because they reduce unnecessary (and therefore wasteful) research practices. As such, environmental considerations are (and should be), at their foremost, a key tenet of best trial (and research question) design and practice.
b. A moral role exists for regulatory/funding/review bodies to lead on addressing trial environmental harm mitigation and adaptation because they have the potential capability to do so with appropriate training and expertise.
c. Many environmental harms associated with conducting HIC-led trials in LMICs relate to capacity issues. An opportunity exists to address these trial-associated harms through LMIC trial site capacity development, which has the co-benefit of mitigating social justice/equity/power issues associated with such trials.
d. Collaboration, addressing power imbalances, and the need to establish trusting relationships both within and between clinical trial actor groups are central to realizing reductions in trial-associated environmental harms and climate vulnerabilities mapped out in points a–c. Such collaboration is a key aspect of relational justice, which recognizes the importance of ensuring that environmental and social safeguards are considered with all affected communities and actors. This includes considerations of, for example, community rights, informed participation and inclusive stakeholder engagement throughout the clinical trial process.
e. An opportunity exists for trials to be underpinned by the principles of resourcefulness, to reduce consumption where possible, and sufficiency, by only collecting and analysing samples and data specifically required to answer the trial research question.

This report sets out key considerations for mitigation and adaptation strategies for climate change (and other environmental harms) covering the key stages of trial activity and defining implementation responsibilities. In terms of mitigation strategies, it makes a number of suggestions for action by policy- and decision-makers involved in trial design and planning; those involved in the conduct of trials; and funders and researchers. It also differentiates between pre-trial, in-trial and post-trial activities.

At the pre-trial stage, the study team's considerations include:

- planning/designing trials using the principles of environmental sustainability and developing policies that avoid research waste;
- providing greater funding for good trial design;
- ensuring clear and early communication between those running the trial and a proposed trial research site (including collaborative trial design);
- reducing (long-distance) travel for feasibility visits and improving local trial capacity when selecting trial sites;
- improving the review of trial applications by providing regulatory guidance;
- driving the implementation of mitigation strategies within the trials and supporting research proposals that include funds for LMIC trial capacity development (funders);
- giving a role for ethics review boards in considering environmental harms associated with trial activities;
- ensuring overall communication between funders, regulators and ethical review boards to clarify expectations on how to conduct environmentally and socially just trials;
- optimizing logistics to reduce waste;
- reducing unnecessary packaging; and
- reporting (or asking for) the environmental harms associated with investigational medicinal products and/or trial-related equipment and supplies.

At the in-trial stage, key considerations include:

- improving staff education and awareness;
- reducing associated environmental harms using a context-specific approach;
- conducting virtual trial meetings when appropriate;
- ensuring that trial protocols allow trial sites to incorporate climate/environmental mitigation strategies;
- providing clear and early communication between those running the trial and trial sites for efficient participant recruitment;
- ensuring maximal retention and intervention adherence to reduce waste;
- reducing travel;
- aligning sample and data collection with the principle of sufficiency;
- ensuring that justification for central processing and storage of samples forms part of review appraisals;
- warming up ultra-low-temperature freezers when feasible;
- reducing on-site trial data monitoring and in-person audits where possible; and
- using green algorithms in data processing.

Key considerations for climate change adaptation strategies across four areas of trial activity: planning and governance; clinical trial facilities; trial participants; and supply chains

At the post-trial stage, key considerations include:

- reducing the use of plastic waste;
- repurposing and/or repairing equipment and repurposing investigational medicinal products to local pharmacies where possible;
- using responsible recycling and disposal of electronic waste;
- using the principle of sufficiency for long-term sample storage;
- adhering to findability, accessibility, interoperability and reuse of digital assets principles of data and sample management;
- adapting the length of archiving of paper documentation to risk level and disposing of paper documents responsibly;
- requiring environmental consideration disclosures in publications; and
- ensuring timely reporting of trial findings, including reporting on environmental impacts and adopting environmentally conscious travel policies.

In terms of adaptation strategies, the report outlines specific elements to consider for climate change adaptation strategies across four areas of trial activity: planning and governance; clinical trial facilities; trial participants; and supply chains.

For the planning and governance area, key considerations include:

- ensuring agility and flexibility of regulatory authorities in order to enhance trial resilience;
- building climate resilience into mainstream considerations for funding decisions;

- providing a role of ethics review boards in ensuring the protection of participant safety in sites with climate vulnerabilities;
- providing a role for trial designers in considering trial climate vulnerabilities and resilient trial design when choosing a trial site; and
- developing appropriate adaptation strategies, including emergency protocols.

For the clinical trial facilities area, key considerations include:

- ensuring awareness of the vulnerabilities of a trial research site and preparation of emergency protocols;
- undertaking routine checks of the trial site's material infrastructure to ensure adherence with vulnerability and adaptation assessments;
- ensuring connectedness of trial sites with larger subnational and national climate adaptation action plans;
- providing staff training on trial site climate vulnerabilities;
- providing effective emergency protocols;
- shifting to renewable energy systems to increase climate resilience; and
- shifting to paperless data clinical trial management systems.

For the trial participants area, key considerations include:

- adoption of contingency protocols for locating and contacting participants and for identifying and meeting participants' trial-related medical requirements; and
- ensuring recognition of the importance of preserving the integrity and validity of the trial where possible.

For the supply chains area, key considerations include:

- conducting risk and vulnerability assessments at every stage of a trial supply chain to help prepare contingency plans in cases of climate shocks; and
- reusing, recycling and repairing trial supplies.

1 Introduction

1.1 Clinical trials

Clinical trials are classified as health research that involves the testing of a treatment or intervention on human participants to determine whether it improves health outcomes *(1)*. Interventions may involve pharmacologicals – such as new drugs or vaccines – or non-pharmacologicals – such as surgery, devices, or educational or behavioural programmes. Trials can test the safety and efficacy of a new intervention against an existing one, or test two existing interventions against each other. The intervention is normally trialled on specific patient populations, although it may be tested on healthy participants (for example, individuals at risk of a health condition). Among clinical trial designs, randomized controlled trials are generally considered the most robust, although non-randomized or unblinded designs may be better suited for addressing certain research questions *(2)*, and more in line with ethics considerations. The number of participants required to take part in a trial depends on the trial type and phase. Trials are typically separated into four phases:[1]

- Phase I studies test new interventions for the first time in a small group of individuals (around 20–80) to evaluate their safety and pharmacokinetics and to identify side-effects.
- Phase II studies test interventions that have been found to be safe in phase I but require a larger group of human subjects (around 100–300) to evaluate proof of concept and efficacy, and continue to monitor any adverse side-effects.

1 It is worth noting that the terminology of "phases" was developed in relation to pharmacological intervention trials, and some debate exists regarding the usefulness of this terminology with regard to non-pharmacological intervention trials *(3)*.

- Phase III trials are conducted on larger populations (around 1000–3000 subjects) to confirm an intervention's effectiveness and continue to monitor side-effects. These trials might also be conducted in different regions and countries; they are often the step before a new treatment is approved for use, and can involve seeking regulatory approval for the intervention.
- Phase IV trials take place after country/regulatory approval, and where there is a need for further testing in a wide population over a longer time frame *(4,5)*.

A useful approach for considering climate (and environmental) mitigation and adaptation of trials is to broadly categorize the process of conducting a trial into three stages, as follows *(6,7)*.

Pre-trial activities are those that occur prior to a trial, including some or all of the following:

- trial design and planning, including trial research site selection and feasibility analysis;
- planning trial protocols;
- securing and training a trial team;
- applying for funding, regulatory and ethics review and approval; and
- equipment and intervention procurement and delivery.

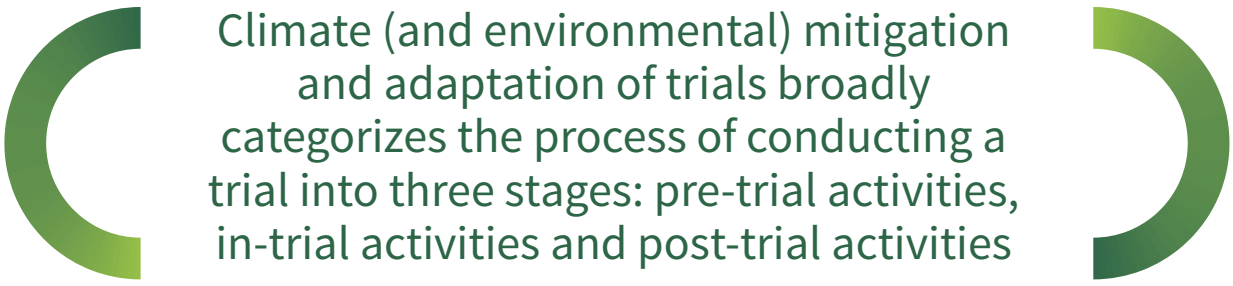
These culminate in the site initiation visit, which launches the trial.

In-trial activities are those that take place once a trial has commenced, including some or all of the following:

- participant recruitment and requesting consent for participation;
- conducting the trial intervention;
- sample/data collection;
- trial-specific participant assessment;
- trial protocol amendments (if required);
- data management and quality monitoring; and
- adverse event reporting.

Post-trial activities are those conducted after a trial finishes, including some or all of the following:

- statistical analysis;
- ongoing data/sample storage;
- return and/or disposal of equipment and intervention;
- archiving and/or destruction of documentation; and
- preparation, publication and dissemination of a clinical study report.



1.2 Clinical trial actors

Table 1 maps out some of the actors involved in a clinical trial, with their roles and responsibilities.

Table 1. Clinical trial actors, roles and responsibilities

Clinical trial actor	Description of roles and responsibilities
Sponsors and their investigator teams	This is the company, institution, group or organization (commercial or non-commercial) that manages and/or finances a trial, and that retains ultimate responsibility for the trial, with the option of delegating specific tasks to any individual or organization that is both willing and capable of taking them on.
Compound/asset/ intervention owner	Depending on context, this may involve several roles, which are not mutually exclusive – for example, sponsor, funder, clinical trial unit (see below) and researcher.
Regulatory authorities	These grant permission for trials that require regulatory approval; they are responsible for these trials' adherence to legal and ethical approvals, oversight and inspections.
Trial funder	These provide financial support for trials. They are responsible for allocating funds to cover trial costs, including staff, interventions, supplies, monitoring and data/sample management. They are sometimes involved in the initiation and management of the trial – especially if they are also the sponsor.
Independent ethics committees (including research ethics committees/institutional review boards)	These ensure that the trial has been designed in an ethically appropriate way that protects the rights and welfare of participants. Responsibilities include reviewing and approving the trial protocol and informed consent documents, and assessing risks and benefits to participants. Relationships between independent ethics committees and researchers should be ongoing.
Clinical trial units (also sometimes called regional coordinating centres)	These are publicly funded; they design, conduct, analyse and publish clinical trials. Their responsibilities include providing centralized management and coordination of the trial, ensuring that it is conducted according to regulatory and ethical standards.
Contract research organizations	These provide outsourced research services to support some clinical trials, including site selection, participant recruitment, and intervention and data management. They can be responsible for ensuring regulatory compliance and/or monitoring trial progress, and for acting as a liaison between the sponsor and other clinical trial actors.
Trial research site and staff	This relates to any public or private entity, agency or medical facility where trials are conducted. They may have multiple roles, including also acting as the sponsor. Staff interact directly with participants and are responsible for recruiting and enrolling participants, obtaining informed consent, conducting study procedures, collecting data, ensuring participant safety and reporting adverse events.
Participants	These are individuals who take part in a trial. Responsibilities include adhering to taking/ using the trialled intervention as required by the trial protocol, attending scheduled visits, and reporting any side-effects or issues. They may also be a patient receiving health care for the condition studied.
Community leaders, community advisory boards, consumer representatives	These are representatives of patients, people who use health services, (potential) participants and the community more broadly; they can advise on the views and interests of communities, and support engagement and recruitment.
Journal editors	These are involved in the publication process of clinical trial results. They are responsible for ensuring that only findings with integrity are published. They can have a gatekeeper role and require certain standards of practice from trial actors.

1.3 Regulatory space

The clinical trial landscape is complex and highly regulated, designed to ensure the safety, effectiveness and ethics integrity of clinical research. It involves essential regulations that guide trial conduct.

For trials testing a new intervention/method that requires regulatory approval (beyond ethics), the regulatory process begins with the clinical trial application – a detailed submission of the trial protocol to regulatory authorities for approval. The Food and Drug Administration oversees regulatory clinical trials in the United States of America, regulating investigational new drug applications and ensuring adherence to good clinical practice while protecting human subjects. The European Medicines Agency governs European Union (EU) clinical trials, reviewing applications and ensuring compliance with regulations. Other countries have their own national regulatory authority, such as the Medicines and Healthcare products Regulatory Agency in the United Kingdom of Great Britain and Northern Ireland and the Pharmaceuticals and Medical Devices Agency in Japan; these approve trial applications, monitor ongoing studies and enforce national regulations.

All trials require ethics approval, which ensures the ethical conduct of the trial, conducted by institutional review boards or research ethics committees/boards. The Declaration of Helsinki *(8)* provides ethics principles for medical research involving human subjects that govern these ethics reviews, emphasizing informed consent, participant protection and risk–benefit evaluation. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use has developed Guideline ICH-GCP E6(R3) for good clinical practice – the international ethical and scientific standard for design, conduct, recording and reporting of clinical trials that involve human participants *(9)*.

The research team responsible for the trial – whether a clinical trial unit, sponsor investigator team or contract research organization – conducts continuous monitoring and auditing to ensure compliance with regulations and protocols; this involves site visits, data verification and safety monitoring.

The clinical trial landscape is complex and highly regulated, designed to ensure the safety, effectiveness and ethics integrity of clinical research. It involves essential regulations that guide trial conduct

1.4 Trials and capacity development in low- and middle-income countries

While clinical trials are conducted globally, they are overwhelmingly conducted in high-income countries (HICs). WHO reported that in 2022 the number of trials registered in HICs (27 133) was over 90 times higher than the figure in low-income countries (294) *(10)*. An article that reviewed all systematic reviews in the Cochrane database related to noncommunicable diseases up to 2011 reported that, of 12 340 trials, 90% were conducted in HICs *(11)*. This aligns with the Global Forum for Health Research publication The 10/90 report on health research, published over 20 years ago, which indicated that while low- and middle-income countries (LMICs) accounted for over 90% of the world's global disease burden, less than 10% of global funding for health research was devoted to addressing diseases and conditions that account for this burden *(12)*.

Some successful efforts have been made to address what has become known as the "10/90 gap" *(12–14)*, but LMICs still lack the necessary health research capacity to inform policy and improve population health *(15)*. The 2024 Access to Medicine Index highlights how companies neglect critical research for diseases like malaria and tuberculosis, which have a significant impact in LMICs *(16)*. As LMICs aim to deliver improved treatments for these diseases through their own capacity development, many of these regions still suffer from inadequate infrastructure and a lack of advanced medical facilities and trained personnel, making it difficult to ensure that trials are conducted to an appropriate standard. Logistical issues such as problems with transportation, supply chain management and data collection are often exacerbated in these areas, and a lack of capacity in material and human resources – as well as in regulatory and ethics review systems – has been reported as a barrier to conducting trials based in LMICs *(17)*.

While changes are under way, LMIC-based trials are still typically led by research teams based in HICs *(15,18,19)*, which often "parachute in" *(15)* resources and expertise, but fail to develop local capacity successfully. These issues compound an ongoing HIC–LMIC power imbalance. Even when material infrastructure is invested in (via refurbishment or building of research sites in LMICs), without the scientific expertise, leadership and retention of human resource investment,[2] these investments can be wasted *(17,20)*. Similarly, clinical trial sample/data storage and processing at LMIC sites may face a lack of infrastructure to house samples and skills to analyse data. Furthermore, because the financial cost associated with capacity-development measures can deter sponsors and research teams, the power imbalance continues between HIC sponsors/research teams and LMIC clinical trial sites. Finally, a lack of investment in local human resources has hindered LMICs setting their own research agendas, which would better address local evidence gaps, be more aligned with local and national health agendas, and produce contextually appropriate health research that can guide health policy *(15)*. This is problematic: such agendas will become increasingly important as the climate continues to change because clinical studies will need to be targeted to generate low-cost and wide-ranging treatment alternatives for affected populations in LMICs.

1.5 Emissions and other environmental harms associated with clinical trials

Approximately 76 000 new trials were registered on WHO's International Clinical Trials Registry Platform in 2023, each producing an estimated 80–2000 tonnes of emissions. Even at the lower end of the estimates, these numbers are significant: 80 tonnes is equivalent to driving a car 12 times around the planet *(21)*, although estimates may vary depending on the type of car. Depending on the trial, clinical trials are also associated with other environmental harms,[3] including the production of hazardous and non-hazardous waste materials *(22)* – such as those from pharmaceuticals *(23)*, air pollution due to road travel *(24)* and water use *(25,26)*.

Work is increasingly being done to quantify and, in turn, mitigate emissions and other environmental harms associated with clinical trials, with an almost exclusive focus on the generation of greenhouse gas emissions (also called carbon dioxide emission equivalents; referred to as "emissions" in this report) *(27–31)*. To date, most reports are from a few HICs, with little published data on how emissions and other environmental harms manifest in different global contexts – particularly in LMICs *(32)*. To avoid being carbon-centric *(33)*,

2 Even with investment in human resources, staff trained in LMIC clinical trial facilities who are not given leadership opportunities and/or key responsibility in trial projects may well leave for opportunities in HICs *(18)*.

3 It should be noted that when considering the environmental impact of trials, this study considers all trial-specific activities over and above routine standard of care, as per Griffiths et al. *(6)*.

this report also discusses other environmental harms including plastic, digital hardware and other waste; land and water use; eco and land toxicity; and particulate emissions.

Most studies identify clinical trial units and investigator teams as a hotspot for emission generation *(6,28,34)*, although the processes studies define as falling under their remits vary. Most include facility energy use and staff travelling to and from work *(31)*, despite using different terminologies *(28)*; some also include activities associated with trial research sites *(31)*, while others do not *(26)*. This report takes the latter approach, differentiating activities associated with clinical trial unit and investigator team facilities and trial research sites (see section 3.2).

Travel has also been identified as being linked with significant emissions: beyond clinical trial unit and investigator team staff-associated travel, this includes trial site staff travel, travel for trial site audit and feasibility/monitoring visits, and participant travel to and from a trial site *(31,34)*. During international trials, or trials taking place in large nations that require internal air travel, the impact of travel is magnified *(31)*.

Laboratory activity can also be an area of concern when considering emissions because of the processing and analysis of biosamples collected during trials, shipment of these samples to external laboratories (should they not be located at the same location as the trial site), and storage of samples – sometimes in freezers at ultra-low temperatures *(31,34)*. Generation of clinical waste can also be associated with environmental harms *(26)*.

Provision of trial supplies is an occasional hotspot *(31,34)*. These include clinical supplies (such as gloves, pipettes, syringes), electronic supplies (including computers, tablets and wearables for participants associated data collection) and other laboratory equipment (scanners, incubators, assay equipment, centrifuges and so on). Provision of supplies involves emissions associated with travel and generation of waste (such as single-use plastic and electronic waste). Supplies also have environmental harms associated with their manufacture (for example, mining and subsequent manufacturing of rare minerals for digital hardware production may lead to toxic and non-toxic waste); these are not comprehensively considered in this report, except where relevant. This report should be read in conjunction with other key WHO documentation and guidelines associated with low-carbon, resilient health-care systems *(35,36)*, including sustainable procurement *(37)*.

1.6 Responsibilities to reduce trial-associated emissions and other environmental harms

While moves to reduce clinical trial-associated emissions and other environmental harms are escalating, ethics scholarship has attended little to questions of moral obligations and responsibilities, although health research ethics scholars more broadly are increasingly arguing that the environmental harms associated with health research ought to be reduced *(38,39)*. Scholars premise this moral obligation in different ways. Ecocentric ethicists argue that the biotic community has moral worth; as such, people's moral sentiments need to extend to this community and the planet they inhabit *(40)*. Relational-based scholars – such as scholars drawing on planetary health, One Health, feminist, traditional ecological and indigenous perspectives – describe the moral importance of the interconnectedness of humans with the land and broader ecosystems, and consider such interrelations to have moral worth *(41–44)*. Anthropocentric ethicists view moral worth as intrinsic only to humans, with obligations associated with the need to preserve the environment as instrumental to sustaining humans – including human health. In the health sector, this anthropocentric view aligns with the key principle of "do no harm", as well as the biomedical ethics principles of beneficence and nonmaleficence *(45)*. Failing to include such considerations, scholars argue, imbalances these principles and ignores the question "health for whom?" *(46)*.

Different justifications have been used to underpin moral obligations to reduce health research-related environmental harms (anthropocentric and/or ecocentric). Pierce and Jameton use a utilitarian argument to emphasize the importance of considering the consequences associated with all aspects of a health sector process – including those associated with the manufacture, use and the subsequent disposal of products. For them, failing to consider this means failing to consider all links within a consequentialist pathway. When these costs are added, they argue that "everyday decisions unquestioned by ethicists and regarded as rational and even praiseworthy may be seen as questionable and possibly maleficent" *(47)*. D'Souza and Samuel have made a similar claim for clinical research *(48)*. Other scholars outside the health research sector ground their arguments in notions of justice – in particular, that justice commitments extend to all those subject to or affected by a specific product/process/technology *(39,49)*.[4] For health research, this includes considering the fair sharing of benefits and burdens across all communities: those involved in the research process, those involved in the manufacture and disposal of products used during the research, and those affected by the outcomes of the research *(49)*.

This moral obligation must also be balanced with notions of social justice (social justice issues beyond those areas already covered by research ethics committees) *(52)* such that it considers the opportunities and barriers associated with reducing trial-related environmental harms in a way that takes into account the context of those already typically marginalized in society/societies. Inter-relational justice offers a useful framework to do this because it goes beyond distributive and procedural justice, arguing that it is important also to attend to relationships between relevant justice subjects. This must be achieved by building trust, respect and dialogue, recognizing that justice goes beyond rules and resources – to the web of relationships that shape how people interact and make decisions together.

Once a moral obligation has been recognized, questions about who should be morally responsible arise *(38)*. Broader ethics scholarship stresses that environmental harms should be addressed through collective responsibilities *(50,53–55)*. The notion of role responsibilities is important here because collective responsibilities are not equal *(38,56)*, but need to be attributed proportionally to ability to perform particular roles.Considerations to reduce trial-associated emissions and other environmental harms must reflect these role positions and abilities to respond. This aligns with sociologists who argue that responsibilities require a capacity to act – that being responsible is being "response-able" (able to respond *(57)*) – and that those who are unable to respond ought not to have a moral obligation to do so.

Finally, the moral obligation to reduce trial-associated environmental harms must be balanced against a possible downstream benefit associated with health research. When considering clinical trials, this might include, for example, an intervention or pathway that can potentially significantly improve health outcomes, or one that limits patient admission to a carbon-intensive intensive care unit *(58)*.

1.7 Decentralized trials and digitalization

Both the Food and Drug Administration in the United States of America and the European Medicines Agency broadly define decentralized trials as trials incorporating digital elements that facilitate the ability for trial activities – particularly the activities of trial participants – to occur at locations other than the traditional trial research site *(59,60)*. This can include, for example, a participant's home, workplace, or local health facility or laboratory. The coronavirus disease (COVID-19) pandemic accelerated the shift to remote trial delivery. Hybrid models blend elements of traditional in-person visits and online or remote visits, while

4 For a broader discussion, see, for example, the work of Iris Marion Young *(50)*, and Nancy Fraser and the "all subjected principle" *(51)*.

full decentralization involves no in-person interaction between the clinician (or trial site staff) and the participant. This latter model uses mobile and medical devices, recruitment and retention platforms, e-visits (replacing face-to-face appointments with online appointments), and video dosing regimens. Trial interventions (both pharmacological and non-pharmacological) are shipped to a participant's home (or delivered virtually in the case of behavioural interventions), along with necessary equipment for electronic data collection *(61)*. Decentralized trials can improve equity and diversity of participation for those who are typically under-represented in clinical trials, by minimizing in-person visits and accommodating individuals with disabilities, older adults and those with childcare duties, while also reaching remote areas and minority groups *(62)*. However, ethics implications and challenges of decentralized trials must also be considered *(63)*, including the fact that such trials may also exclude certain communities and/or populations who may be digitally excluded.

Relevant to this report, decentralized trials have the potential co-benefit of reducing trial-associated travel emissions *(64)*. However, decentralized trial-related challenges exist, including access to technology – particularly in LMICs and in underserved or less digitally literate communities in HICs, where participants and/or staff may lack the necessary devices, digital literacy and/or internet connectivity. Protecting participant information and ensuring privacy can be complex, and for multicountry trials, regulation may differ across borders. Finally, it is uncertain whether decentralized trials would increase environmental harms associated with preparing packaging, moving samples and gathering data from multiple locations.

1.8 Climate change resilience and adaptation

Climate change resilience refers to a system's capacity to anticipate, respond to, cope with, recover from and adapt to climate-related shocks and stress *(65)*. Adaptation is a related concept, defined by the Intergovernmental Panel on Climate Change as a "process of adjustment to actual or expected climate and its effects. In human systems, adaptation seeks to moderate harm or exploit beneficial opportunities. In natural systems, human intervention may facilitate adjustment to expected climate change and its effects" *(66)*.

Minimal attention (in both HICs and LMICs) has been paid to the climate resilience of clinical trials. This is the capacity of clinical trial systems to anticipate, respond to, cope with, recover from and adapt to climate-related shocks and stress. As the climate changes, clinical trials are likely to become increasingly vulnerable to, for example:

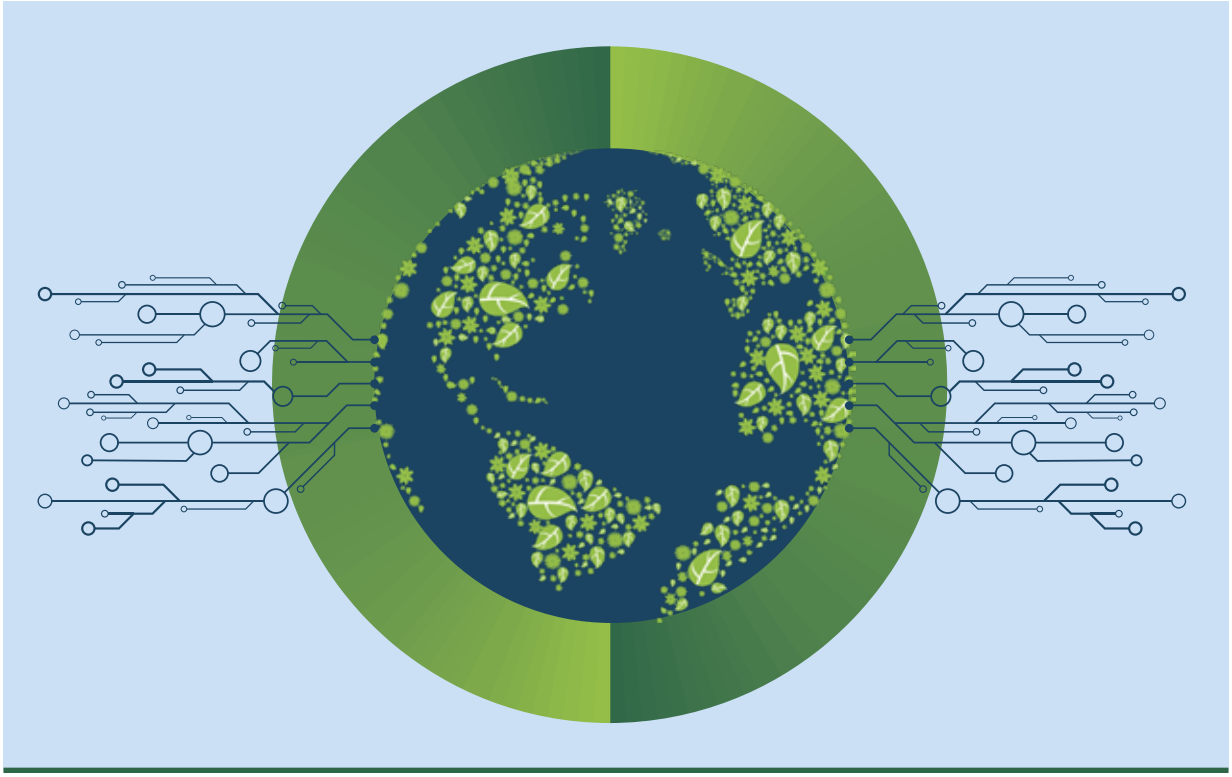
- increased flooding or other weather events that can preclude participants and/or staff attending trial site facilities;
- damage to clinical trial research sites and facilities; and/or
- disruption to supply chains – and in particular cold chains – that affect the delivery of equipment and/or drugs and medications.

Such current or future threats are likely to be particularly relevant to LMICs, which are disproportionately exposed to the effects of climate change because they have fewer resources to protect against them, despite their minimal contribution to historic global carbon emissions *(67,68)*, raising issues of justice.

1.9 Structure of the report

Chapters 2 and 3 describe pre-trial, in-trial and post-trial activities, and the opportunities and barriers associated with changing these activities to drive a reduction in trial-associated climate and other environmental harms. Chapter 4 focuses on resilience capacity and current and future adaptation in clinical trials, including for four areas of activity: planning and governance, trial facilities and infrastructure, trial participants, and supply chains.

2 Methodology



2.1 Collaborative, iterative and co-produced research

This report was compiled collaboratively, in a way that reflects the views of a wide group of clinical trial actors. Initially, the study team spoke to clinical trial actors with a range of expertise across a number of countries and disciplines, asking about their perceptions, attitudes and experiences of the opportunities and barriers associated with mitigating the climate and other environmental harms associated with clinical trials, and the climate resilience of clinical trial systems (Table 2). To develop a first draft of this report, the findings were compiled with an extensive literature review. The first draft was shared with the initial interviewees to seek: overall feedback, clarity around certain topics and further suggestions.

After compiling initial feedback, the report was shared with further actors in the clinical trial space for additional feedback. Further contributors (two from Australia, one from Argentina, one from France, one from Switzerland and one from the United Kingdom) were identified through snowballing and through the MRC-NIHR Trials Methodology Research Partnership Greener Trials group *(69)*. Following a second round of feedback, the near final report was shared with all contributors for final reflections.[5] All individuals who provided feedback and/or commented on the report were invited to be listed as a report contributor, although many chose not to accept.

5 Feedback was continuous throughout the second round, as a live web-based document was used to draft the report, with contributors adding to the document when time permitted.

Table 2. List of actors consulted and their roles

Country of residence (Number of actors)	Trials represented by actors consulted (Number of actors)	Roles of actors consulted
• Brazil (3) • Denmark (1) • Ethiopia (1) • Gabon (1) • Germany (1) • India (1) • Kenya (3) • Malaysia (3) • Netherlands (Kingdom of the) (2) • South Africa (2) • United Kingdom (8) • Zambia (1)	• Infectious disease (tuberculosis, HIV/AIDS, malaria, Chagas, Ebola, Marburg) (14) • Sickle cell disease (1) • Oncology (3) • Cardiology (5) • Respiratory medicine (2) • Physiotherapy (1) • Psychology (2) • Gerontology (1)	• Infectious disease (tuberculosis, HIV/AIDS, malaria, Chagas, Ebola, Marburg) (14) • Sickle cell disease (1) • Oncology (3) • Cardiology (5) • Respiratory medicine (2) • Physiotherapy (1) • Psychology (2) • Gerontology (1)

2.2 First phase of discussions with trial actors

Clinical trial actors were identified based on the authors' existing networks via snowballing, and by searching established trial networks for contacts. For the latter, the study team consulted a WHO database, and identified and contacted actors from different networks, including:

- Trials of Excellence in South Africa
- East African Consortium for Clinical Research
- Central African Network on Tuberculosis, HIV/AIDS, and Malaria
- Pan African Consortium for the Evaluation of Antituberculosis Antibiotics
- Academic Research Organization Alliance for Southeast and East Asia
- Oxford University Clinical Research Unit
- Mahidol Oxford Tropical Medicine Research Unit Tropical Health Network
- Zika Preparedness Latin American Network.

The study team spoke to 27 individuals (10 women and 17 men) for 30–70 minutes. A schedule of questions (see Annex 1) guided discussion, although a flexible approach ensured that conversations could be informal, to develop an understanding of the issues within different contexts and regions.

2.3 Synthesis of report

Post-conversation discussion notes were analysed for themes to assist the initial writing phase. These notes guided a literature review, which placed the themes within the broader context of clinical trials. As such, this report does not represent a description of the conversations with trial actors; rather, it is a synthesis of those conversations, combined with further input from these actors, the literature review and insights from additional contributors who were invited to review the draft document.

2.4 Limitations

Limitations of this report relate to the following exclusions.

Certain processes related to clinical trials were excluded. The report excludes environmental harms associated with the manufacture and use of interventions being trialled (pharmaceuticals, digital and/or other interventions) and any products used during the trial (i.e. it does not include embodied emissions). This includes (non-comprehensive) considerations of:

- designs that reduce environmental and climate impacts;
- energy-efficient medical devices;
- minimally invasive technologies that might have lower environmental impacts;
- development of interventions that mitigate radiation and cytotoxic or other hazardous processes/products as much as possible;
- investigational medicinal products that are developed and manufactured in line with broader planetary concerns through planetary health and One Health approaches, with consideration of, for instance, antimicrobial resistance;
- devices and/or drugs with increased shelf-life that will last longer and could reduce the need for transportation; and
- considerations associated with the most environmentally sustainable intervention method.

WHO can play a role in developing guidelines around the most appropriate intervention approaches *(70)*.

Certain clinical trial actors were excluded from shaping the report. Some areas of the clinical trial landscape are either under-represented or not represented – notably, clinical trial funding bodies and regulators, and clinical trial actors based in North and Central America. There was also over-representation of contributors currently focused on infectious diseases, and more generally over-representation of actors focused on trials with pharmacological interventions versus non-pharmacological interventions.

Analysis of national regulations and guidelines on pollution prevention, health-care waste management, and end-of-use and sustainable disposal practices – such as take-back policies and environmentally sound waste technologies – was excluded. All of this material will be vital for national policy-makers to consider alongside the considerations identified in this report. The study team did, however, conduct a document review of legislation, regulations and guidelines governing clinical trials in WHO Member States to explore whether and how environmental sustainability was mentioned. This is reported in Annex 2.

3 Mitigating emissions and other environmental harms associated with clinical trials

3.1 Pre-trial activities

Pre-trial activities include:

- trial sponsors' and their teams' activities, including trial design and planning, and the selection of the trial research site;
- a review of a trial proposal, including by regulators, funding bodies and/or ethics committees; and
- ordering trial supplies.

3.1.1 Sponsors' and their teams' activities

Before clinical trials are conducted, considerations regarding whether a trial should take place, and how it should be conducted are crucial to ensure that the trial generates high-quality, robust clinical data. Such questions are pertinent to environmental considerations, given that redundant or poorly designed trials waste resources and produce climate and other environmental harms with few health gains. Chalmers and Glasziou proposed what has become an oft-cited figure of 85% of biomedical research amounting to waste *(71)*, which in trials relates to unregistered, unreported, biased, inadequately designed and/or unpublished trials *(72)*.[6]

6 The study team recognized that there may be context-specific barriers that compound such issues, particularly in LMICs, but these are beyond the scope of this report.

3.1.1.1 Trial planning

It has long been advocated that redundant trials can be avoided by purposeful adherence to systematic reviews of existing evidence *(73)*, and that many clinical trials fail to follow this most basic tenet (72). Redundant trials[7] not only expose participants to undue risk but lead to resource waste/unnecessary environmental harm. Redundancy can be reduced by ensuring that the trial is answering a research question that cannot be answered by existing evidence *(71,72)*. Furthermore, non-relevant research questions can lead to difficulties in recruitment and retention of trial participants, increasing the likelihood of trial failure *(74)*, and furthering the chance of wasted resources/environmental harm. For example, when a research question explores a health condition or area of disease that a particular population does not value, this population's interest in participating in the trial may be lacking.[8] Thus, research questions need to be valuable to local populations.

These responsibilities do not sit solely with trial planners; they are shared by funders, ethics review boards and regulatory bodies, which need to ensure that research questions are both valuable to local populations and not redundant (see section 3.1.2). Further, within an LMIC context, a perceived lack of coordination between funders, sponsors, research organizations and regulatory bodies means that the likelihood of redundant research taking place is higher *(15)*. WHO best practice recommends consortium/platform models as a way to develop capacity while reducing the risk of research redundancy *(76)*.

3.1.1.2 Trial design

Trial design refers to how a trial is conducted. Rigorous trial protocols ensure a trial's quality and validity – as well as participant safety – increasing the likelihood of a successful trial, and thereby reducing the chance of research (and therefore environmental) waste. Adequately powered, double-blind randomized controlled trials are widely regarded as the gold standard in clinical research, offering the highest level of evidence for evaluating interventions *(77)*. Despite this, a large number of trials are poorly designed. Yordanov et al. *(78)* claimed that 42% of clinical trials amounted to wasted research due to inadequate methods – for example, lack of blinding or exclusion of participants from analysis. A failure to employ adequate research methods during trials problematizes findings and the systematic reviews that include them, leading to "erroneous" conclusions by researchers, which in turn can generate further wasted research.

In another example of poor trial design, trialists may use unstandardized laboratory testing of biological samples with a lack of standardized approaches. While there are many standardized clinical laboratory measurement procedures, which form a critical end-point of many trials, newer procedures often differ between laboratories; this can lead to flaws in the aggregation of data and, in turn, to flawed clinical practice guideline development *(79,80)*. If clinicians are unaware of this in the planning and design phases, trial data will be flawed – something that is both financially and environmentally wasteful *(79)*. While some sponsors might choose to use centralized laboratories in order to limit exposure to this risk, this comes with its own environmental burden (see section 3.2.5).

Beyond ensuring trial rigour, trials must be environmentally sustainable by design. Environmental impact assessment tools can help to achieve this. Some tools are in development, such as the Sustainable Healthcare Coalition's Clinical Trial Carbon Calculator, which is oriented to industry trials, and is in beta testing at the time of writing *(81)*. Meanwhile, Griffiths et al. *(31)* have published detailed guidance on how to conduct a

7 As per Chalmers & Glasziou *(71)* and Kim & Hasford *(72)*, this report considers a clinical trial redundant if it intends to investigate a question that can be "answered satisfactorily with existing evidence". See Kim & Hasford *(72)* for further discussion on this issue.

8 For more examples of poorly formulated research questions see Fandino *(75)*.

carbon footprinting assessment of a publicly funded clinical trial. These existing tools, and future tools to come, can help trialists assess and try to mitigate emissions as much as possible.

Certain innovative trial designs may have the co-benefit of improving trial convenience and/or quality, while also reducing environmental burdens. Decentralized trials are a good example (see section 1.7). Other examples include point-of-care and nested trials, which draw on existing data to record outcomes, thereby reducing environmental harms associated with data collection. Virtual or in silico trials could be used to help plan and design trial protocols by helping to predict trial outcomes and to design drugs/interventions, which may ultimately increase research value and reduce research waste *(82)*. There is also growing interest in using such trials to generate synthetic data (to mimic real data), and therefore reduce the need for real data, reduce sample size and reduce research waste. As yet, this technology is still a promise, and no standards exist.

However a trial is designed, it should consider local context (culture, health infrastructure, availability of medical personnel and climatic conditions), and should optimize the use of available resources through effectiveness and efficiency to ensure that protocols are easy to implement in low-resource health facilities. Protocols should also consider accessible alternatives to reagents/equipment that cannot be sourced locally – alternatives that may be more feasible and less costly (environmentally and financially) than sourcing original reagents/equipment from overseas (resourcefulness).

> A large number of trials are poorly designed – 42% of clinical trials amounted to wasted research due to inadequate methods such as lack of blinding or exclusion of participants from analysis

3.1.1.3 Feasibility visits and site selection

The trial team and/or sponsor conducts a feasibility assessment – usually in person – when selecting a trial research site. Considerations include the site's potential participant demographics; recruitment potential; site infrastructure, including equipment; staff and digital aspects; and perceived site quality. Extra feasibility visits may be conducted at specific LMIC trial research sites if concerns arise about the ability of the site to manage the scale of the trial, and/or high staff turnover and lack of continuity in leadership roles. In some instances, a lack of trust may lead to new trial sites being activated to conduct a trial *(83)*. This often requires longer trial site staff training periods, and may involve external consultants and contract research organizations, with associated extra travel from different countries. Furthermore, sponsors may conduct individual regulatory and audit visits for these new sites, even if the site is in use by other sponsors, increasing travel burdens. While local contract research organizations may conduct these visits, large, international contract research organizations might not have local offices in LMICs, and trust concerns may arise that more local organizations lack the ability to perform feasibility checks to the required standards.

Capacity development offers the co-benefit of improving the standard of LMIC trial sites and/or local contract research organizations, while reducing emissions associated with extra feasibility visits to newly activated trial sites, or pre-existing sites (perceived to be) lacking in material or human resources. Greater local clinical trial capacity would also allow LMIC clinical research sites to host more locally led clinical trials. Capacity development, however, is often a secondary goal for trial design, if a goal at all *(15)*. While instances of capacity development exist *(14,84,85)*, important gaps remain that could be filled by funding bodies (see section 3.1.2.2).

3.1.1.4 Ordering trial supplies

Trial supplies are materials supplied to a trial site for trial use, including ancillary equipment (gloves, pipettes, syringes and so on); diagnostic tests and associated reagents (such as lateral flow immunoassays and larger equipment such as X-ray machines, scanners and assay equipment); digital-related equipment (including laptops and wearable health devices); and/or the investigational products (the drugs being tested). The scope of this report does not include environmental harms associated with the manufacture of trial supplies, although it is worth noting that preliminary research suggests that supply provision has a small impact on trial emissions. This is despite such supply chains contributing substantially to carbon emissions in the broader health sector.

> Increased use of digital data requires increasing data collection, storage and processing, all of which requires energy consumption which, if fuelled by fossil fuels, can increase carbon emissions

Priorities for addressing health sector supply chain mitigation and adaptation more generally have been reported *(86)*. This is important, as Griffiths et al. *(6)* highlight certain instances countering the fact that supply chains are low contributors to clinical trials, including a trial in which the provision of 360 digital tablets for completion of questionnaires was responsible for nearly 50% of the trial's emissions. As trials become increasingly digitized – with ever more use of electronic data collection from tablets, smartphones, personal medical devices (such as glucometers) and wearables (such as smart watches *(87)*) – such emissions and other environmental harms associated with digital technologies need to be considered. Increased use of digital data requires increasing data collection, storage and processing, all of which requires energy consumption which, if fuelled by fossil fuels, can increase carbon emissions. Beyond emissions, the problematic reliance on single-use plastics *(88)* – often pronounced because of the need for those conducting new trials to order large amounts of supplies from the outset – is also an issue, especially because supplies are often over-packaged in plastic *(89,90)*. The quantity of trial-used single-use plastics is not well documented, but single-use plastic consumption by the wider medical field is estimated to be approximately 2% of global plastics production (by financial value) *(88)*. Plastic-associated environmental harms include the emissions generated by the oil used in their production, land and aquatic pollution, and human toxicity and ecotoxicity *(90,91)*. Trials can consider switching to reusable medical devices and glassware, opting for biodegradable bioplastics and/or ensuring that plastics are correctly disposed of, with a preference for recycling where possible *(88)*. Conducting an initial environmental impact assessment may help to identify any hotspots. Furthermore, while supply chains are viewed as small contributors to clinical trials overall, it is important to remember that such studies often do not include the manufacture of investigational medicinal products within calculations, and may potentially exclude other manufacture associated environmental costs.

While supplies may have a small impact on a trial's associated environmental harms, shipping of supplies may increase these impacts, so optimizing shipping logistics is important. At the same time, LMIC trials have specific issues – for example:

- supplies may not be available locally, or sponsors may mandate that a certain non-local supplier must be used, increasing shipping emissions;
- over-ordering of supplies is often required to mitigate extended waiting periods for shipments because of logistical difficulties with supply chain infrastructure;

- a lack of local skills and/or engineers to use and/or service supplied equipment means that engineers need to be flown in to train personnel; and
- when equipment breaks (minor or major problems), HIC-based skilled engineers must travel to the trial site to fix machines.

3.1.2 Reviewing trial proposals

3.1.2.1 Regulatory bodies

Regulators can play a crucial role in any collective effort to accelerate implementation of mitigation strategies within clinical trials – including providing clear guidelines, communication and support, along with purposeful coordination between regulators and other clinical trials actors. WHO has already called for regulatory support for the introduction of more sustainable pharmaceutical products and services *(92)*.

However, international regulation does not currently consider trial-associated climate and/or environmental harms. Furthermore, while regulation is crucial for safe and effective trial conduct, it can present barriers to mitigating a trial's climate/environmental harms: regulators are often perceived to impede the running of clinical trials *(93)*, or have a lack of desire to address shifting practices and innovation within trials proactively – including innovations that could reduce environmental harms. Alongside this, sponsors often adhere over-cautiously to clinical trial regulation. This amounts to a reluctance to deviate from established clinical trial norms, or to include practices that incur lower environmental harm – even in cases where these practices are not strictly required by regulation – because of concerns that they will be penalized for implementing strategies that are not "common" practice.

In LMICs, overly complicated regulatory systems, long delays in waiting for regulatory approval and a lack of sufficiently skilled authorities in regulatory agencies can significantly disrupt trials before they begin, with reports of grants expiring before approval is attained *(17)*. Trial delays may disincentivize sponsors, limiting capacity-developing efforts, with the possibility of a negative feedback loop and the co-harm of increased travel requirements to LMIC trial sites (see section 3.2.6). Furthermore, many clinical trials, even when conducted in LMICs, adhere to the regulatory standards of major international regulatory agencies (such as the Food and Drug Administration and European Medicines Agency), requiring trial processes – such as sample storage and analysis – to be conducted in locations outside the country, typically in HIC laboratories, adding to emission burdens. Nevertheless, it is worth noting that the number of regulatory authorities considered to be stable and well functioning by WHO is increasing in LMICs *(94)*, and there is an increasing move for national regulators to push back against the release of samples to centralized facilities, especially when considering biobanking samples after the study.[9]

3.1.2.2 Funders

Governments, charities, independent funding bodies, pharmaceutical companies, sponsors (typically in industry-led trials) and academic institutions all support clinical trials. Industry-funded trials predominate *(97)*, although public funding (governmental, government-aligned or independent health research funding organizations) plays a vital role, providing an opportunity for these funders to encourage the mitigation of trial-associated environmental harms.

In other health research sectors *(98)*, calls have been made for environmental harm considerations to be

9 The biobanking landscape is taking an interest in mitigating its associated environmental harms (95,96).

embedded into requirements for funding proposals *(99)*. Indeed, some large public funding bodies already implement such requirements, including Wellcome *(100)*, while other funding bodies in some HICs have signed up to the Heidelberg Agreement on Environmental Sustainability in Research Funding (101). The example set by the inclusion of patient and public involvement – now a routine aspect of clinical research in the United Kingdom and some other countries – and the greater attention now given to research impact and to equity, diversity and inclusion issues in research could provide important parallels for building environmental concerns into mainstream funding requirements *(58,102)*.

Funders can also incentivize environmental harm mitigation by allocating specific funds in clinical trial research grants to environmental mitigation strategies, such as allowances for investment in digital infrastructure required for conducting decentralized trials, financial incentives for low-carbon travel options and funds for environmentally minded procurement *(103)*.

Finally, funders can play a role in LMIC trial capacity development to facilitate locally led LMIC trials. This could have the potential co-benefit of reducing international trial-related travel associated with HIC-led LMIC trials because a lack of financial capacity has been reported as one of the most significant barriers to conducting clinical trials in LMICs *(17,19,104)*. While LMIC researchers and trial research sites can secure funding through collaboration with HIC institutions and research *(15,18)*, these collaborations are typically led by the HIC partner, and in many cases are perceived to perpetuate inequities in the HIC–LMIC partnership, while failing to sustainably develop LMIC clinical trial capacity. Franzen et al. *(15)* have argued that this often relates to material infrastructure investments that ignore the necessary human capital to sustain local research priorities (see sections 1.5 & 3.1.1.3).

3.1.2.3 Ethics review

As human participant research, clinical trials require ethics approval. Given ethics review boards' remit to consider the risk/benefit ratio of trials while protecting participants, potential exists to expand this role into explicitly evaluating the environmental (and consequential human) harms associated with trial activities. Building these considerations into the regulations and guidance that govern review boards has been suggested elsewhere *(105)*. A precedent exists for this: some LMIC ethics review boards already incorporate the need for capacity-developing measures to be built into clinical trial design *(106)*, suggesting that environmental concerns could also be built into considerations when approving a trial. However, ethics review boards may lack expertise to do this. Furthermore, in LMICs, ethics review systems often lack capacity – with overly bureaucratic and hierarchical governance structures, and a lack of skilled individuals, leading to bottlenecks in trial approval *(17,18)*.

3.2 In-trial activities

3.2.1 Clinical trial unit/investigator team activity

Clinical trial unit/investigator team[10] facilities are a trial emissions hotspot because of the energy associated with both running the offices and staff travel to and from the facility. Reducing facility energy

10 This report draws a distinction between clinical trial units and sponsor investigator teams, which is the terminology used throughout, to demarcate the fact that clinical trial units are typically involved in publicly funded trials, while industry-sponsored trials typically use their own investigator teams (or employ the services of a contract research organization). It should also be noted that clinical trial unit/investigator team activity commences in the pre-trial phase and continues throughout the course of a trial; however, in order to differentiate it clearly from trial research site activity, it is placed in the in-trial activities section of this report.

consumption and/or switching to renewable power sources (see section 3.2.2), is an appropriate emissions mitigation strategy. However, many units/teams are housed within larger institutions that have control over energy source decisions. Capacity-building and training for staff involved in clinical trials on climate and environmental considerations should be viewed as good practice.

Clinical trial unit/investigator team staff can be incentivized to use low-carbon travel and/or hybrid working practices to reduce emissions *(6)*. Furthermore, where appropriate, necessary trial investigator meetings – which involve sponsors, research teams, unit/team members, and trial site investigators and staff – can be held virtually to help eliminate travel emissions. However, poor digital and/or public transport infrastructure may prevent these options in certain LMICs: context is crucial and each unit/team has specific needs that require tailoring of climate/environmental mitigation strategies with the use of environmental assessment tools (see section 3.1.1.2). This tailoring is crucial to ensure that LMIC trial sites are not disadvantaged because they lack the ability to implement certain mitigation strategies. Rather, sponsors, research teams, unit/team members, and trial site investigators and staff should work collaboratively to customize suitable approaches.

Finally, it is worth nothing that LMIC health-care facilities (including those that host clinical trial unit/investigator teams) may already operate under resourcefulness in response to lacking human and material resources *(107,108)*, resulting in the development of innovative, low financial – and accidentally environmental – cost solutions. For example, fewer full-time staff trained as well-rounded experts rather than more part-time staff with specific limited skills may mean lower staff travel requirements. There is an opportunity for knowledge exchange from these LMIC trial sites to HIC-based trial teams.

3.2.2 Trial research site activity

Clinical trial unit/investigator teams and trial research sites have similar emission sources, including site utility use and staff commuting, but with some key differences. First, staff travel at trial sites may be more difficult to reduce because it involves face-to-face trial-specific participant meetings. Decentralization can address (some of) this, but barriers might preclude this in LMICs (see section 3.2.4). Second, trial sponsors (whether academic or industry) design stringent protocols to ensure a trial's rigour, validity and participant safety, with which trial sites must comply: environmental harms can only be considered if part of the protocol. Such considerations are very rarely included, meaning that if innovative solutions are developed at the trial site they cannot be implemented.[11] Third, a lack of incentives exists to incorporate more expensive low-emission or low-resource options when trial sites compete for business. All of these issues – and particularly the second and third – can be exacerbated by a power dynamic in which LMIC research facilities must present themselves as a cost-effective and trusted site to HIC-led trials.

At the same time, some trial site practices may (accidentally) already mitigate emissions through the principles of resourcefulness discussed above (see section 3.2.1) – particularly when sponsors are working to a budget or the trial sites are based in LMICs. Examples include sharing reagents to reduce leftovers, reusing equipment that might otherwise be disposed of unnecessarily and washing hands as a substitute for plastic gloves where appropriate. Where resourcefulness strategies are not already utilized, consideration should be given to introducing mitigation strategies – particularly when considering energy use. This might include switching off lights in trial site facilities when not in use, running large equipment (such as X-ray machines) on appropriate power settings and switching these machines off when not in use. As such, clinical trial protocols should be designed in ways that allow trial research sites to incorporate

11 Note considerations 5, 22 and 23 in section 3.3.4 for research trial sites to have collaborative input into protocol design.

mitigation strategies, including any resourcefulness strategies, where possible.[12]

Meanwhile, for LMIC trial research sites considering renewable power sources, local considerations around energy availability and reliability are required, as well as assessments of renewable power infrastructure costs. Renewable power offers an excellent opportunity for LMIC health-care facilities, which have historically suffered problems with electrification *(109)* – not only as an environmental mitigation strategy that can have an overall net benefit for local health care but also as a cheap power source, particularly for solar energy *(110)*. Such power may also offer an alternative to diesel-fuelled back-up generators, although it may not always be suitable because of the time taken to fire up and the need for extended use; here, biofuels offer a useful alternative. For HIC trial sites, renewable energy may also represent an opportunity to mitigate emissions associated with energy use, although similar considerations around infrastructure costs are required.

3.2.3 Participant recruitment and retention

Participant recruitment and retention is a well-known issue in trials, leading to delays in start and/or completion dates and inflation of costs. Further – perhaps most importantly in terms of environmental harms – it can threaten the viability of the trial because of invalid or inconclusive results *(111,112)*. It has been reported that 37% of trials fail to meet their target sample size, with 11% failing to recruit even a single participant *(113)*. Among its other benefits, patient and public involvement has helped to boost recruitment and retention of participants (*111,114)*. Trial design can also improve recruitment, with adaptive trials for cancer treatment and tuberculosis enabling evaluation of multiple agents/regimens with lower overall participant numbers *(115)*.

Nevertheless, issues remain, and environmental harms associated with these delays include:

- repeat feasibility visits from monitoring teams to ensure that a trial site is prepared to re-commence (see section 3.1.1.3);
- continued accumulation of emissions at a clinical trial unit/investigator team site; and
- expiration of trial supplies, including the investigational product (if a drug), laboratory kits and/or diagnostic tests – supplies that may need to be re-shipped if not locally available, and which have their own environmental harms associated with production and manufacturing.

Participant recruitment and retention is a particular issue in LMICs and for certain disease types *(17,116)*. A host of interventions and elements have been proposed to address these issues, including three key examples. First, attention needs to be given to participant study materials and consent forms so that participants are well informed about study requirements. Second, novel approaches to recruitment through electronic health records maintained by local or regional health-care facilities could be investigated. Finally, the trial design could support recruitment and retention in LMICs and remote regions, which may lack infrastructure (medical, transport, digital) – including minimized study visits and remote or local assessments, potentially using electronic health records and routinely collected data where possible *(117)*.

At the same time, the environmental burden associated with digital technologies, including data records, should not be ignored: a life-cycle assessment of a large eye hospital in India showed that electronic health records come with a significantly larger carbon footprint compared to keeping paper records owing to the electricity use of associated data storage requirements *(118)*. Considerations regarding how these issues should intersect broader requirements around gender and other equities in trial participation should be taken

12 Maintenance of water, sanitation and hygiene systems is also of critical importance for a clinical trial site, but it falls outside the scope of this section of the report. It is discussed further in section 4.3.

into account, alongside the assurance of community rights and inclusive engagement throughout the clinical trial process.

3.2.4 Trial-specific participant assessments

Trial-specific participant assessments are one of the largest trial emission hotspots because of participants' associated travel *(6,119)* to trial sites to complete enrolment documentation and provide their consent to take part in the research, to undergo diagnostic testing, to receive trial-specific treatment and/or interventions, and for evaluation and monitoring purposes. The environmental impact of the travel depends on its mode and distance. This, in turn, depends on the location of the trial site relative to a participant's residence; the sophistication of local/national public transport infrastructure; the participant's social, personal and economic situation; and their preferred mode of travel. Well-connected trial sites where trial participants live locally may well promote public transport use. Trial sites further from participants, who may be more rurally located, are likely to require more car travel. This latter situation may be exacerbated in LMICs, which have fewer viable sites capable of hosting trials, meaning the need to travel further, with potentially poorer public transportation infrastructure. These issues can lead to missed assessments, delaying a trial and leading to wasted resources (see section 3.2.3). Gender and other factors may also play a role in transport decisions, and considerations of individual and community rights through inclusive engagement must be taken into account.

The elimination of participant (and potentially staff) travel to a trial site through decentralized trials *(61)* offers one possibility to reduce the environmental harms. It also has other potential benefits, including reducing the practical and time burdens for participants, lowering financial costs, and simplifying logistical issues *(61,120)*. Participants can be educated about the potential environmental benefits. However, decentralized trials also come with concerns: they may not straightforwardly relieve trial burden for participants, who become responsible for aspects of a trial that were previously handled by trial staff – such as maintaining and operating the digital technology required to facilitate electronic data capture or inputting data on digital data platforms *(121)*. Furthermore, in cases where decentralized trials include mobile health care, depending on how this is organized, it may not necessarily reduce total travel because of continued health-care staff and participant travel. Finally, it is uncertain whether decentralized trials would increase environmental harms associated with preparing packaging, moving samples and gathering data from multiple locations.

While digitalizing trials has been argued to reduce emissions by up to 90% *(122)*, this is dependent on whether the digital equipment is already in place or needs to be specifically procured (see section 3.1.1.4). Digitalization is also hindered in LMIC settings because of a lack of consistent internet access and possible low rates of digital literacy *(123)*. Concerns have also been raised regarding the security and quality of patient data. Critics have pointed to the vulnerability of wearable technologies and potential weak points in digital data platform security *(124)*, as well issues surrounding wearables' ability to measure certain quantitative clinical parameters accurately *(125)*. Other concerns include participant access and ability to use digital technologies, which may intersect gender and other equity concerns.

Beyond travel-related emissions, the way trial-specific participant assessments are designed can also reduce environmental harms: they should be designed using the principle of sufficiency – only assessing that which is needed to answer the research question, and in a way that allows for standardization and comparability. As Griffiths et al. *(6)* argue, "heterogeneity in what and how outcomes are measured contributes to research waste which in turn increases emissions due to the need for further studies to be able to answer the research question". They also note that "the inclusion of core outcome sets, reflecting outcomes of critical importance to decision-makers including people with lived experience, can reduce such research waste and thus provide an opportunity to reduce emissions across the sector as a whole".

3.2.5 Sample collection, analysis, transport and storage

The collection of biosamples is a critical aspect of trialling a new or existing drug intervention. Climate and other environmental harms associated with this process are dependent on how samples are collected, transported and stored. For example, poor phlebotomy technique can lead to wastage of phlebotomy tubes that cannot be reused owing to safety concerns *(126)*. Overcollection of samples – in terms of both the volume of samples and the volume of biomaterial collected for a given sample – also presents a concern *(127–130)*. Trialists often collect biosamples "for collection's sake" because of their perceived potential to offer future value, even if in excess of necessary requirements to answer the trial's research question. Extra clinical time is required for collection and processing of these samples; extra material (plastic tubes, trays) is required to store them; and energy is required to maintain them at low temperatures. As such, no extra collection of samples/data should occur other than that included in the trial design, in line with the principle of sufficiency. However, in certain cases – such as with rare or risky-to-collect sample types – collecting samples that are surplus to current requirements may be justified. In this case, collection must be justified at the planning stage, and samples must not be collected ex post unless with further scrutiny from regulators/funders and/or ethics review bodies. This could reduce future waste because it minimizes the requirement for further collection through a future trial.

Low- and ultra-low-temperature sample storage is a well-known energy cost during all forms of clinical research. Ultra-low-temperature freezers, which typically operate at temperatures of −80 °C and below, and liquid nitrogen, which operates at temperatures of −196 °C, are particularly energy-intensive equipment *(130,131)*. "Warming up" – a strategy that typically involves changing the "standard" operating temperature of an ultra-low-temperature freezer from the scientific norm of −80 °C to −70 °C – can save energy demands *(130)*. However, this comes with a greater risk to samples in the case of power loss *(132)* – a particularly prevalent issue in LMICs due to unstable electric grids *(109)* – because samples will take less time to warm up, meaning that their safety, quality and viability may be compromised.[13] In such cases, LMICs can use diesel-fuelled back-up generators, but this further contributes to environmental harms *(133)*.

Cold chain logistics associated with transporting samples also have associated environmental harms. While a paucity of research still exists in the biomedical sector, studies in food transport cold chain logistics have shown that refrigeration elements can contribute up to 40% of a transport vehicle's engine emissions *(134)*. A 2014 review estimated that the lower, more rigorous temperature controls required for medical goods would produce even greater emissions.[14] Furthermore, globally, transport refrigeration units continue to use hydrofluorocarbon refrigerants (such as R404a) with large global warming potential, making refrigerant leaks a significant concern *(135)*. In LMICs, where cold chain infrastructure is often lacking, dry ice may be used instead *(136)*. However, recent volatilities in dry ice supply have caused shortages in local supply and drastic price rises *(137)*, meaning that shipments must be ordered from non-local suppliers, increasing travel-associated emissions. Cold chain infrastructure is likely to become an escalating issue as climate change increasingly leads to rising temperatures.

If LMIC-based laboratories lack the requisite equipment to conduct relevant diagnostic tests, samples may be shipped from LMIC-based trial sites to out-of-country testing facilities. Sometimes, even very basic tests that could be conducted locally are conducted out of country due to a perception that this will lead to more trusted

13 How much difference exists between warming up times following a power cut at −80 °C and −70 °C remains a point of contention; however, existing evidence suggests that −80 °C provides more sample security through longer warming up times, albeit only a marginal amount over short periods (see Farley et al. *(132)*).

14 Bozorgi A, Zabinski J, Pazour J, Nazzal D. Cold supply chains and carbon emissions: recent work and recommendations [unpublished working paper]. 2014 (https://doi.org/10.13140/RG.2.1.1343.6000).

results, and that samples will be wasted if not analysed in a HIC laboratory because they will not be analysed to their full capacity. Furthermore, HIC-based trial sponsor teams and/or regulators may ask for clinical trial samples to be repatriated to the sponsor team's country for storage owing to investigator preferences. In other instances, this may be deemed crucial because there is a lack of storage capacity at LMIC sites. Justification for central processing and storage of samples should be part of review board appraisals, in conjunction with capacity-development investment in local or regional central storage banks.

Once collected, samples are shipped to the laboratory for testing and analysis, which uses laboratory equipment and reagents, and requires staff travel, all of which are covered in other sections of this report.

> A 2014 review estimated that the lower, more rigorous temperature controls required for medical goods would produce even greater emissions

3.2.6 On-site data monitoring and site audits

While data monitoring[15] is an essential part of all trials to ensure validity *(138)*, trial-specific travel for the purposes of on-site monitoring contributes heavily to trial-associated emissions – particularly in cases of HIC-led trials in LMICs, where on-site monitoring is frequent and often requires long-distance travel. From a strictly environmental perspective, any move to reduce on-site monitoring or associated travel is beneficial. However, barriers remain. First, industry-led trials, in particular, have been accused of driving a certain "conservatism" to monitoring clinical trials *(138)*, employing a cautious reading of clinical trial regulations and good clinical practice guidance. They also tend to adopt a "more is better" logic to on-site monitoring and source data verification,[16] which assumes that data entry and processing errors will be better detected by this hyper-vigilant approach. For such actors – and others, because this strategy is widespread – this approach ensures against the cost of trial findings being rejected by regulators. Despite this (over-)cautious approach, however, research indicates that risk-based monitoring and central monitoring[17] offer viable alternatives without sacrificing data integrity *(138–140)*. For sponsors conducting large-scale multicentre trials, central statistical monitoring allows analysis of large datasets to facilitate the identification of atypical data entries and risk-points *(141)*. While such strategies may add extra time for site staff – particularly those in LMIC contexts, who may need to scan documents for review – and while digital tools and large-scale data processing have their own environmental costs *(142,143)*, many clinical trial actors have called for a shift from source data verification towards these other approaches, given their overall benefits *(144)*.

15 The point is often made that monitoring does not always begin neatly with the initiation phase of a clinical trial. For the purposes of this report, however, issues that could equally be applied to monitoring carried out in both pre- and post-trial settings are covered in the in-trial activities section.

16 On-site monitoring here refers to when monitors (typically contract research associates or members of the research team) visit trial research sites in person. Source data verification is the process by which reported clinical trial data are compared to original source records.

17 Risk-based monitoring refers to monitoring certain risk-prone activities rather than a 100% source data verification approach, in which all data are checked even if they are not deemed to present a higher risk. Central monitoring refers to monitoring that takes place from a central – usually remote – location, in which data are collected via digital means and then analysed and verified by a central team, who are usually members of the research and/or sponsorship team. This is usually in contrast to or in place of on-site monitoring.

However, embedded cultural norms may contribute to continued on-site monitoring and site audits. Industry sponsors and contract research organizations still often employ intensive on-site monitoring visits *(145)*, suggesting that some of the environmental benefits conferred by central statistical monitoring are being lost to unnecessary over-caution. While the COVID-19 pandemic helped to demonstrate the feasibility of central monitoring, many clinical trial actors still feel that certain features of an in-person site visit cannot be replicated through digital solutions. In-person site audits, for example, are often perceived as allowing auditors to "get a feel" for a laboratory and catch details that might not show up in a digital audit visit *(146)*. This is particularly the case for LMIC-based trials because of the perceived and actual clinical trial capacity issue, meaning that more frequent on-site monitoring is necessary to ensure that the trial is running according to stringent protocols and standards. This lack of capacity typically includes a lack of skilled staff experienced in running trials *(17,18)*, high staff turnover in research sites *(147)*, a lack of digital infrastructure required to conduct central monitoring effectively and unreliable grid systems that affect the ability to conduct such monitoring *(109)*. These real capacity gaps combine with perceived capacity gaps and a lack of trust from HIC partners *(148)* to drive the desire to conduct on-site monitoring and site audits.

Clustered visits – visiting several closely distanced sites at a time to reduce flying – can reduce travel, but are not always possible, particularly in certain LMIC contexts in which trial sites are remote and difficult to reach. Furthermore, sometimes travelling directly between two close LMICs is more expensive than flying via a more distant HIC. The use of local contract research organizations allows for more frequent on-site monitoring visits while reducing the travel miles necessary to conduct these visits. However, similar capacity-based issues present again, in as far as HIC partners have reported poor experiences of using local contract research organizations due to a lack of skilled personnel *(149)*.

3.2.7 Data processing and algorithms

Artificial intelligence and machine learning tools are already being used to identify potentially eligible trial participants and for data monitoring *(150)*. Use of artificial intelligence algorithms is also being explored as a future tool for analysis of clinical trial data *(151)*. With increasing use of such tools, trial actors should collect, store and process data only for purposes necessary to answer their research questions, and in line with the principle of sufficiency. Environmental harms associated with the digital sector are well documented; they arise from the mining, manufacture and disposal of digital hardware, as well as the energy use associated with data storage and processing – including use of machine learning *(142,143)*.

Tools are available to calculate emissions associated with machine learning (and other artificial intelligence) computation, which can help researchers understand and mitigate the impact of ongoing data analysis as much as possible *(143)*. Adherence to the findability, accessibility, interoperability and reuse of digital assets (FAIR) principles of data management *(152)* can ensure that the value of existing clinical trial data is maximized, thus reducing future clinical trial redundancy and unnecessary future data analysis.

Visiting several closely distanced sites at a time can reduce travel, but are not always possible, particularly in certain LMIC contexts in which trial sites are remote and difficult to reach

3.3 Post-trial activities

3.3.1 Return and disposal of supplies

The return and disposal of trial supplies have environmental impacts, but these are less well accounted for than their provision and manufacturing, partly because much of the harm is associated not with emissions but with issues of land use, human toxicity, particulate emissions and ecotoxicity. These harms can relate to the disposal of single-use plastic clinical supplies, digital hardware waste (e-waste) from laboratory equipment,[18] and the destruction of the investigational medicinal products, reagents and other hazardous materials.

For large trial equipment, such as ultra-low-temperature freezers, proper processing at a waste disposal centre in required to capture environmentally harmful hydrofluorocarbon gases used as refrigerants *(130)*. If not disposed of properly, e-waste can lead to land pollution, human toxicity, and ecotoxicity *(153)*. Larger, widely used laboratory equipment should also be disposed of responsibly; this should be explicitly planned in trial designs. Where possible, all equipment (including digital hardware) should have its life-cycle extended through repurposing and repair *(154)*, including purchasing repurposed pieces of equipment for trials, where possible, and use of take-back policies.

Clinical trial sponsors have a responsibility to destroy unused investigational medicinal products in accordance with local regulations and good clinical practice, ensuring that the products' destruction does not result in environmental contamination. Repurposing unused stocks of investigational medicinal products (which are often drugs able to be utilized by local pharmacies, particularly in LMICs) can minimize trial waste. This is only possible for medicines that have regulatory authority and are locally in demand – not for products that are as yet unlicensed.

3.3.2 Storage of samples and data

Trialists must adhere to jurisdictional requirements about length of sample storage. The length of long-term post-trial sample storage affects a trial's associated emissions. For example, storage of biosamples for a 10-year period following the conclusion of a multicentre, international clinical trial significantly contributed to the carbon footprint of the trial *(31)*. As discussed in section 3.2.5, the same perception of the future research value of biosamples that drives the collection of samples "for collection's sake", can also drive a desire to store samples for long periods of time. No extra unnecessary long-term storage should occur except if samples are considered to be of potentially high value. Sample and container volumes should also be minimized. As for data, adherence to the FAIR principles of data management *(152)* can ensure that the value of existing clinical trial data is maximized, thus reducing future clinical trial redundancy and unnecessary future data analysis *(155)*.

3.3.3 Archiving and destruction of documentation

A trial's activities, processes and organization – including trial protocols, participant recruitment forms, consent forms and case report files – must be stored for a certain length of time, varying from 5 to 25 years *(156)*. These have traditionally been documented on paper – and still are, particularly in LMICs.

While archival storage space usually has smaller trial-associated environmental harms than other trial

18 While national and international regulations around e-waste are increasing, much still ends up in LIMCs, where it is informally recycled and reused in ways that can be harmful to both the environment and human health.

hotspots, long-term storage of large numbers of archival documents is associated with additional trial emissions *(6)*.[19] Shredding followed by recycling is the most environmentally friendly destruction method for documents, but in some places documents are burned, or sent to landfill and then burned. Burning of paper is associated with production of aerosol pollutants and environmentally harmful particulate matter *(157)*.

Documents are increasingly being digitized – particularly in HICs where digital literacy, connectivity and infrastructure are more developed *(158)*. The shift towards "paperless" trials, which significantly reduce paper use, represents an opportunity to streamline time-consuming trial processes, such as validation of source data off site *(159)*. It is often touted as a means to decrease clinical trial costs and inefficiency *(160)*. However, the logistics of shifting to electronic systems – such as clinical trial management systems – requires resources, infrastructure and training, with additional cost burdens *(161)*. Frequent power outages in LMICs can hinder device charging, and use of diesel back-up generators increases fuel consumption. Furthermore, electronic case reports – which are designed in HICs to collect participant data – are not context specific, driving an increase in errors in other settings; site-specific prompts are lost and/or local requirements for good documentation practice are not implemented on tablets. Hybrid paper/digital approaches can increase complexity and cost without improving efficiency, and may only reduce paper use slightly while resulting in additional environmental impacts associated with digitization and data processing. This is especially the case if tablets are procured specifically for individual short-span research projects. Given that digital waste (e-waste) recycling infrastructure continues to remain inadequate and/or unregulated in many countries – particularly in LMICs – discarded devices frequently end up in landfill or e-waste dump sites. As such, before digitalizing, consideration should be given to minimizing e-waste as much as possible.

3.3.4 Dissemination of results

In the context of this report, dissemination includes the reporting of trial results in a public database in accordance with established reporting guidelines, such as the SPIRIT-CONSORT guidance *(162)*, as well as peer-reviewed conference and journal publications. Disseminating trial findings is a critical aspect of the research process: it reduces the likelihood of unnecessary trial duplication, permits replication of results (where necessary), and facilitates inclusion of the results in future meta-analyses and systematic reviews.

Unreported or poorly reported clinical trials represent a form of research (and therefore environmental) waste. They are examples of poor clinical practice, and are unethical in regard to research participant time. Some research has shown that a cross-section of unreported trials registered on clinicaltrials.gov represented around 87 000 participants *(163)*.[20] Regulatory bodies, ethics review boards and funders can have a role in implementing stricter policies on reporting *(164)*. Examples might include regulatory bodies requiring mandatory reporting of clinical trials, and the restriction of funding to sponsors unable to verify the reporting of previous trials. Clinical trial reporting should, where possible, be open access *(165)*.

During reporting, emissions associated with conference travel have associated environmental harms. Research teams should consider the geographical locations of conferences (prioritizing local locations), low-carbon modes of transport and the number of research staff attending. When trials include such individuals, priority should be given to early-career researchers, those based in LMICs or those based in low-resource settings, for whom such travel will be valuable for their career progression.

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19 The archiving of trial documents is associated with other burdens, including space constraints on trial centres. This can lead to outsourcing to third parties, which places an additional financial burden on trial sites.

20 Many of the issues concerning attention to methodological issues by those responsible for a trial, which also helps to avoid reporting concerns, are discussed in sections 3.1.1.1 and 3.1.1.2.

Table 3 maps the study team's specific proposals for climate change (and other environmental harm) mitigation strategies across the three stages of trial activity. It should be noted that in some trials, some actors may hold more than one responsibility.

Table 3. Study team proposals for climate change (and other environmental harm) mitigation strategies

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Pre-trial activities			
Trial planning and design			
1. Clinical trials should be planned to reduce research waste *(76)*.	This relates to whether a trial should be conducted. Unnecessary trials lead to research (and therefore environmental) waste. • Systematic reviews should be conducted to prevent the conduct of redundant trials and minimize research waste. • A relevant research question will maximize the trial's likelihood of generating high-quality, robust clinical data and minimize research waste. A research question that is valuable and applicable to local populations has the co-benefit of increasing likely recruitment and retention rates (see section 3.2.3). • All planned trials must be registered on an international clinical trial registry to avoid unnecessary duplication of studies.	Those who plan trials	This is also a good opportunity to consider how the research question aligns with broader global sustainable development goals.
2. Clinical trials should be designed to reduce research waste.	This relates to how a trial will be conducted. Trials must be designed around the "right first time" approach, using rigorous methodologies to produce research of clinical value, minimizing research (and therefore environmental) waste. • Verification and validation of approaches within trial design, sound and valid measurement practices, statistical analysis and standardization are all required. • Identification and active development of standards are needed where lacking – including for document management, trial methodologies and use of equipment – especially when innovative approaches are being used.	Those who design trials	–

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Pre-trial activities			
Trial planning and design			
	• Wherever possible, clinical trials should be sufficiently powered. • Trials should be designed in line with SPIRIT-CONSORT guidance *(162)*. *Note:* in specific cases such as ultra-rare diseases, it may be difficult to reach a sufficiently powered sample size. In this situation, an alternative design (such as a Bayesian trial) may also be considered.		
3. Policies that target research waste reductions should be developed.	Research waste leads to environmental waste. Possible policies to reduce research waste could include: • a requirement for systematic reviews as part of a funding application process; • a requirement to use risk of bias tools during trial design (such as Cochrane RoB 2.0) *(166)*; and • including a methodologist during trial design.	The regulatory authority National and international funders	An evidence base can ensure that policies that target research waste reductions do not backfire, leading to overly bureaucratic processes that have little impact *(167,168)*.
4. More funding should be provided for expertise in good trial design.	Good trial design is more likely to produce research of clinical value and minimize research (and therefore environmental) waste. Funding could help to increase: • expertise in clinical trial methodology through supporting trial methodology initiatives (such as the MRC-NIHR Trials Methodology Research Partnership *(69)*) to support capacity/capabilities, including considerations around measurement validity, reliability, accuracy and standardization; and • promotion of knowledge through funding networks for knowledge exchange *(166)*.	National and international funders Local governments	Environmental, financial and scientific co-benefits are gained from improved trial methodology. For example, funders have access to a larger pool of peer reviewers with appropriate expertise to ensure that trial methodologies are of an appropriate standard in funding proposals. *Note:* the MRC-NIHR TMRP Statistical Analysis Working Group peer reviewed pre-prints during the COVID-19 pandemic to ensure that in times of urgent research, methodologies remained rigorous *(169)*.

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Pre-trial activities			
Trial planning and design			
5. Clear and early communication are needed between those running the trial and a proposed trial research site, including collaborative trial design.	Clear and early communication is likely to improve trial design, decreasing the likelihood of research waste, because it: • improves the strength of the partnership, encouraging collaboration, skills transfer and efficient study execution; • identifies risks that inform the risk assessment process and therefore what a risk-based approach to monitoring would be, so that trial teams can consider the need for on-site monitoring (which is associated with environmental harms; see section 3.2.6) or alternative strategies earlier; • ensures that those designing the trial have knowledge about the likelihood of recruitment issues, reducing the risk of inappropriate trial design or failure of the trial to recruit, meaning that it closes early without results – each of which, in turn, could lead to poor trial outcomes and research waste; and • increases trust between partners, potentially reducing the need for additional feasibility/training visits (see consideration 7).	Those who design trials Those who will run the trial The proposed trial site	Clear and early communication also helps to develop clinical trial capacity. In cases of HIC-led LMIC trials, this process can redress power imbalances in HIC–LMIC trial relationships. However, open questions include whether processes that redress such power imbalances actually have the co-benefit of reducing on-site monitoring.
6. Trials should be designed and funded using the principles of environmental sustainability by design.	Use of environmental impact assessment tools can be helpful during trial design, as some mitigation strategies may be more expensive and will need to be built into funding proposals. Tools currently in development include the industry-oriented Sustainable Healthcare Coalition's Clinical Trial Carbon Calculator *(81)* and the carbon footprinting assessment for publicly funded clinical trials proposed by Griffiths et al. *(31)*. Funders should support researchers currently developing educational, quantification and accreditation tools that can enable clinical trialists to understand the environmental impact of their work.	The regulatory authority National and international funders	Regulators need to implement clear guidance about acceptable and unacceptable strategies for trial design. An evidence base is needed to ensure that such designs also maintain trial quality. LMIC trial sites should not be pressured to pursue mitigation strategies should this incur a prohibitive cost to the site.

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Pre-trial activities			
Trial planning and design			
	Trials design should also consider the principle of resourcefulness. Many LMIC trial research sites may already be using resourceful approaches that can be shared with HIC trialists. Once funded, a trial kick-off meeting and ongoing communication is needed to discuss how the operationalization of the designed mitigation strategies – developed prior to funding – will be implemented in practice.		
Feasibility visits and site selection			
7. As far as possible, (long-distance) travel for feasibility visits should be reduced (see section 3.1.1.3).	This can be reduced by: • conducting a risk-based assessment to confirm whether a feasibility visit is required and, if the risk is low, considering allowing the site to complete a feasibility questionnaire instead; • planning feasibility visits alongside other trial-related travel (cluster visits) where logistically possible; • using local contract research organizations, training monitors or similar to conduct feasibility visits for international trials, or for remote trial sites in larger countries; and • using real-time meeting technology (including cameras) with detailed assessment documentation to provide robust evaluation of sites.	Trial designers Those running the trial The regulatory authority – to implement clear guidance around necessary/ unnecessary site visits	Some LMICs may lack the infrastructure/digital literacy required to conduct remote visits, so trial design must reflect this. Some local contract research organizations in LMICs are sometimes perceived as lacking in the necessary skills to perform feasibility visits by HIC researchers.
8. Local trial capacity should be improved to limit feasibility/ training visits.	Capacity is required to improve the trial skills and understanding of local research staff. This is particularly the case in LMICs, but is also relevant for disadvantaged areas of upper-middle-income countries. By developing capacity and training the sites, less monitoring and fewer on-site visits are likely to be required, and/or they can be alternated with virtual visits (see consideration 7).	Funders	Responsibilities also include actors outside the trial landscape. Involvement at the government level is crucial, and needs to be supported through WHO and similar organizations (such as the Pan American Health Organization).

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Pre-trial activities			
Ordering trial supplies			
9. Logistics should be optimized to reduce waste and allow for poor supply chain infrastructure.	Poor supply chain logistics must be taken into account to ensure that supplies arrive as expected, to: • prevent over-ordering of stocks that may end up wasted; and • ensure that investigational medicinal products, reagents, diagnostics and other supplies do not arrive after expiry dates, leading to waste. Investigational medicinal product digital display labels can facilitate real-time updates of expiry dates and protocol numbers, potentially reducing waste.	Trial sponsors Drug manufacturers, distribution companies and suppliers	Ongoing issues may be associated with poor transport (and supply) infrastructure in LMICs. Responsibilities are broader than the trial landscape. Investigational medicinal product digital display labels are likely to be too costly for use by most publicly funded trialists and trialists in LMICs. Funders need to support use of costly mitigation strategies if there is evidence of clear benefit (see consideration 14).
10. Plastic waste should be reduced as far as possible.	Where possible, use of biodegradable plastics (if in line with current recommendations for health research), reusable equipment and/or glassware over single-use plastics reduces trial-related plastic waste.	Those designing the trial Those running the trial Research sites and laboratories	In some LMICs, governments are not incentivizing a reduction in plastic consumption. Biodegradable plastics are a relatively new innovation and may be less widely available.
11. Unnecessary packaging should be reduced.	This is necessary for both investigational medicinal products and trial-specific reagents, materials and equipment.	Supply manufacturers Trial sponsors	–
12. If possible, the environmental harms associated with the investigational medicinal products and/or trial-related equipment and supplies should be reported (or asked for) *(170)*. *Note:* even though the environmental harms associated with investigational products are outside the scope of this report, the study team does see a responsibility to ask questions about these harms to build awareness about the issues and drive change.	Reporting provides a clearer understanding of the intervention's environmental harms, allowing cost–benefit reflections on the likely long-term impacts on the patient care pathway following the trial. Note: even if the environmental burden of investigational medicinal product manufacture is high, it might be outweighed by downstream environmental benefit relating to the future care pathway.	Trial planners and designers to ask for information Drug and equipment manufacturers to provide information The regulatory authority	Open questions remain about how to leverage sustainable practices with drug and/or equipment manufacturers.

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Pre-trial activities			
Reviewing trial proposals			
13. Regulators should provide guidance on the acceptability of trial mitigation strategies to remove possible regulatory ambiguity, with the understanding that such approaches need tailoring to the trial context.	Clear guidelines, communication and support are needed from regulators about the acceptability of proposed mitigation strategies. Furthermore, unambiguous guidance on the use of innovative (low-emission) trial methods is needed, including for decentralized, point-of-care and adaptive clinical trials, as well as use of established surrogate outcomes *(171–174)*. Without clear guidance, sponsors are likely to remain cautious, with a reluctance to include these practices because of concern about penalization *(58)*.	The regulatory authority	Regulators may be unaware of the climate (and environmental) impact of clinical trials, and may require training to develop capacity and expertise in this area. Further research is needed to determine the content of such guidelines and evidence on the safety and quality of these approaches. LMICs may lack much of the infrastructure/digital literacy to introduce decentralized trials and other trial approaches, and trial design must reflect this. It is also unclear whether digitalization could result in digital exclusion of certain participant demographics. This is particularly important if local regulation limits the use of sensitive data. Those LMICs that have digital infrastructure need training in decentralized methods. Open questions remain about who is responsible for this. It is uncertain whether decentralized trials would increase environmental harms associated with preparing packaging, moving samples and gathering data from multiple locations.
14. Funders should drive the implementation of mitigation strategies within clinical trials.	Funders should require (as a minimum) that researchers incorporate environmental considerations into funding proposals so that such considerations are embedded into the awareness and/or behaviours of trialists. These can be in narrative form, and can be assessed as acceptable/unacceptable before or during the peer-review process. This would be similar to requirements for other areas of research, such as equity, diversity and inclusion.	Funders	Funders have produced statements of intent to address the environmental harms associated with research *(175)*, but these are generally from HICs. Funders must consider that it may be more difficult for those in LMICs to implement some environmental mitigation strategies into trial

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Pre-trial activities			
Reviewing trial proposals			
	Funders could also incentivize incorporation of environmental considerations by allocating specific funds in research grants for environmental mitigation strategies. This could include allowances for investment in digital infrastructure for conducting decentralized trials, which would facilitate: • more decentralized trials, thereby reducing participant travel to appointments; • more working from home where appropriate, thereby reducing staff travel; and • better connectivity to allow international clinical trial meetings and data checking/validation online. Allowances could also cover investment in: • financial incentives for low-carbon travel options; • funds for environmentally minded procurement; and • processes that lead to trial-associated environmental harm reductions, but that may be costly to implement without funding (see consideration 9).		design, and/or such strategies may negatively affect social inequities (for example, with travel to conferences; see consideration 42). It is also unclear whether digitalization could result in digital exclusion of certain participant demographics. Funders (and sponsors, who are likely to review funding proposals of colleagues) are likely to lack resources and/or expertise in assessing environmental considerations. It is uncertain whether decentralized trials would increase environmental harms associated with preparing packaging, moving samples and gathering data from multiple locations.
15. Funders should support research proposals that include funds for LMIC trial capacity development.	Capacity development could reduce the need for travel to LMIC research sites in HIC-led trials because it would increase local expertise (for example, in fixing machines and having skilled trial personnel). It should include material (laboratories/equipment), human (skills/expertise/leadership) and regulatory/ethical review capacity.	Funders	No case studies have been conducted at present. Capacity development has the co-benefit of promoting locally led LMIC trials; however, an open concern remains that many countries still have regulatory gaps (in standards, provisions and laws) that need addressing, without which clinical trials cannot be conducted. Responsibilities associated with capacity development include other actors outside the trial landscape.

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Pre-trial activities			
Reviewing trial proposals			
16. Ethics review boards could consider the environmental harms associated with trial activities.	Given these bodies' remit to consider the risk/benefit ratio of clinical trials, this role could also consider the environmental (and consequential human) harms associated with trial activities.	Ethics review boards	Ethics review boards may lack resources and/or expertise in assessing environmental considerations. Uncertainties remain about how reviewers could make these assessments. Ethics review boards are unlikely to be able to reject peer-reviewed and funded trials. Input is limited to commenting on potential mitigation strategies. Capacity development – particularly in LMICs – could support this, but this may not be a priority.
17. Communication is needed between funders, regulators and ethical review boards on expectations around how to conduct environmentally and socially just clinical trials, so that all trial actors clearly understand expectations *(103)*.	Clinical trial actors are interconnected – what one group does has impacts on others. Coordination across sectors is essential to ensure consistency and alignment, and to minimize unnecessary demands on and confusion for trialists. Clinical research networks and discipline- and disease-specific consortia can coordinate parties, accelerating evidence generation and reducing waste *(76)*.	The regulatory authority Funders Ethics review boards	Clinical research networks and consortia have a co-benefit of helping capacity development in LMICs *(76)*.

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
In-trial activities			
Clinical trial unit activity (or activity of the investigator team running the trial)			
Note: here a distinction is drawn between clinical trial units and sponsor investigator teams (the terminology used throughout the report) to demarcate the fact that clinical trial units are typically involved in publicly funded trials, while industry-sponsored trials typically use their own investigator teams (or employ the services of a contract research organization).			
18. Education and awareness-raising of staff should be undertaken.	Capacity-building and training for staff involved in clinical trials on climate and environmental considerations should be viewed as good practice.	Managers of clinical trial unit/ investigator teams (commercial/ non-commercial) Institutional facilities Contract research organizations (as part of their service)	–
19. Where possible, clinical trial unit/ investigator team facilities' associated environmental harms should be reduced using a context-specific approach.	Such harms can be reduced by: • switching to/using renewable power sources; • reducing facility energy consumption by changing staff behaviour; • ensuring that all equipment uses appropriate power settings; • turning off equipment (computers and other machines) when not in use; • switching off facility lights when not in use; and/or • promoting reductions in staff travel-associated emissions (for example, by allowing flexible/hybrid working).	Clinical trial unit/ investigator teams running the trial Institutional facilities	–
20. Where appropriate, necessary trial meetings should be conducted virtually.	Virtual meetings can reduce emissions associated with travel.	Clinical trial unit/ investigator teams running the trial	–

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
In-trial activities			
Trial site activities			
21. Education/ awareness of staff should be undertaken.	Raising awareness and providing education on trial-related environmental harms helps implementation of strategies.	The Trial site managers	–
22. Where possible, site facilities' associated environmental harms should be reduced.	This can be through: • switching to/using renewable power sources; • reducing facility energy consumption by changing staff behaviour; and/or • promoting reductions in staff travel-associated emissions (e.g. allowing flexible/hybrid working).	The trial site The institutional facility	LMIC trial sites may already employ resourceful management techniques (due to resource unavailability) that are low in environmental harms.
23. Trial protocols should allow trial sites to incorporate climate/ environmental mitigation strategies.	This should include clear and early communication between sponsors, investigator teams, clinical trial units and a trial site, with collaborative input from trial site staff around resourceful on-site practice.	Trial designers The trial site The regulatory authority – to implement clear guidance around appropriate or inappropriate strategies	–
Participant recruitment and retention			
24. Clear and early communication is required between those running the trial and trial sites to ensure efficient participant recruitment, maximal retention and intervention adherence to reduce research (and therefore environmental) waste	Communication must include collaborative input from trial site staff around context-specific barriers and enablers to recruitment and retention. This ensures that these barriers and enablers are considered in the design of the trial. Innovative methods of recruitment and retention and intervention adherence should be considered, including use of electronic health records maintained by local or regional health-care facilities to identify eligible patients and for collecting trial data. Trial designs should support recruitment and retention in LMIC contexts and remote regions, which lack infrastructure (medical, transport and digital), including minimized study visits, remote or local assessments, point-of-care assessments and use of existing data.	Trial designers Those running the trial The trial site	–

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
In-trial activities			
Trial-specific participant assessments			
25. Where possible and appropriate, participant (and potentially staff) travel to a trial site should be reduced.	Elements of decentralized trials should be adopted where appropriate. Point-of-care trials and nested trials that draw on existing data to record outcomes can decrease travel associated with assessments.	Trial designers The regulatory authority – to implement clear guidance around appropriate or inappropriate trial approaches and strategies	Open questions remain around ensuring security and quality of data collected by digital means. The potential for digital or other exclusion of patients would need to be considered on a case-by-case basis for the population, location and method of decentralization of the trial. It is uncertain whether decentralized trials increase environmental harms associated with preparing packaging, moving samples and gathering data from multiple locations.
Sample collection, analysis, transport and storage			
26. Sample and data collection should be aligned with the principle of sufficiency.	No extra collection of samples/data should occur other than that included in the trial design, in line with the principle of sufficiency. When collecting data, standardized core outcome sets should be used as recommended in WHO's Guidance for best practices in clinical trials *(76)*, without excessive secondary/tertiary outcomes. Heterogeneity in what and how outcomes are measured leads to research (and therefore environmental) waste *(6,176)*. If some samples are considered of potentially high value, even if not related to the research question, collection and storage must be justified at the planning stage and not be collected ex post, unless it is with further scrutiny from regulators/ funders and/or ethics review bodies.	The trial planner/ designer Those running the trial Funders/ regulatory authority/ethics review boards reviewing the trial	In certain cases, such as where the samples become part of an accessible biorepository and/or with rare or risky-to-collect sample types, collecting surplus to requirement samples is justified (see section 3.3.2). This could reduce future waste because it minimizes the requirement for further collection through a future trial.
27. Justification for central processing and storage of samples should form part of review appraisals	Central processing increases trial emissions because of shipping requirements, and should be avoided where possible. Capacity-development investment in local or regional central sample storage banks should be a part of trial funding.	Funders	–

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
In-trial activities			
Sample collection, analysis, transport and storage			
28. Ultra-low-temperature freezers should be "warmed up" where feasible.	Where possible, trial sites and laboratories can save energy by warming up ultra-low-temperature freezers from −80°C to −70°C.	Trial sites and laboratories The regulatory authority – to provide clear guidance on sample storage temperatures	Power outages and grid instability might mean that trial sites are reluctant to warm up their freezers due to shorter emergency reaction times associated with concerns about sample integrity (see section 3.2.5 for a more detailed discussion).
29. Correct maintenance of ultra-low-temperature freezers should be ensured.	Proper maintenance of ultra-low-temperature freezers can considerably increase energy efficiency and extend a unit's life-cycle.	Trial sites and laboratories	–
On-site data monitoring and site audits			
30. Where possible, on-site data monitoring of the trial should be reduced.	Use of risk-based, remote, central and/or statistical data monitoring offer viable alternatives without sacrificing data integrity *(138–140)*.	Trial designers Those running the trial	–
31. Where possible, in-person site audits should be reduced.	Where possible, conducting remote, virtual site audits can reduce travel-related emissions.	Trial designers Those running the trial	A certain amount of in-person site audits might remain necessary, as remote visits cannot provide access to all the elements that must be checked. Over cautious perceptions of LMIC trial sites, combined with real capacity gaps, may drive more frequent in-person site audits by HIC research teams. Funding may be required to provide experts and equipment to LMIC trial sites where virtual site audit capacity is underdeveloped.
Data processing			
32. Green algorithms should be used where possible.	Tools are available to calculate emissions associated with machine learning (and other forms of artificial intelligence) computation, which can help researchers understand and mitigate as much as possible the impact of using such methodologies *(143)*.	Those running the trial	–

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Post-trial activities			
Return and disposal of supplies			
33. Equipment should be repurposed and/or repaired.	Widely used laboratory equipment, such as ultra-low-temperature freezers, can often have their life-cycles extended through repurposing and repair.	The research site	Repurposing and repair services may be lacking in some LMIC locations (154).
34. Responsible recycling and disposal of e-waste should be undertaken.	If purchasing digital technologies (computers, tablets and smart phones) for short-term trials, repurposed equipment should be purchased. At trial completion, reuse, recycling or, if necessary, responsible disposal should be ensured.	Trial designers Those running the trial The trial site The regulatory authority – to provide clear guidance regarding this	Lack of recycling infrastructures and expertise in many countries, particularly in some LMICs.
35. Unused investigational medicinal products should be repurposed to local pharmacies, where possible.	Repurposing unused stocks of investigational medicinal products, which are often locally used drugs, can minimize trial waste.	Those running the trial The trial site The regulatory authority – to provide clear guidance regarding this	This is not possible for as yet unlicensed investigational medicinal products – only for medicines that have regulatory authority and are locally in demand.
Storage of data and samples			
36. Long-term sample storage should align with the principle of sufficiency.	No long-term storage should occur, except that made transparent and justified in the trial design, and reviewed by funders and ethics committees.	Those running the trial The trial site	In some cases – such as where the samples become part of an accessible biorepository, or the samples are associated with risky-to-collect sample types – long-term storage may be justified.
37. .FAIR principles of data and sample management (152) should be adhered to.	FAIR principles can maximize the value of trial samples and data while reducing unnecessary future research.	Those running the trial The trial site	–
Archiving and destruction of paper documentation			
38. The length of archiving should be kept to a minimum.	The length of time required for archiving paper documentation should be risk-based, such that long archive times are not required for low-risk trials.	The regulatory authority	The length of time is defined in the regulations, but regulators could be encouraged to consider this.

Table 3. Study team proposals for climate change mitigation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Post-trial activities			
Archiving and destruction of paper documentation			
39. Responsible disposal of paper documents should be ensured.	Paper trial documents should be shredded and recycled when disposed of, rather than sent to landfill or burned.	Those running the trial	The disposal of paper documents may need to adhere to local regulations.
Publication and dissemination			
40. Publication and dissemination.	This would build awareness around the issue.	The trial site Publishers Those running the trial	Open questions remain about what these considerations should/ could include (and how much detail would be required).
41. All trial findings should be reported in a timely manner.	Unreported trials (including negative findings) represent a form of research waste, and are examples of poor clinical practice. Publications should be open access, including datasets where possible or information about how to request access, and all trial results must be published on an international clinical trial registry. Regulatory bodies, ethical review boards and funders have a role in implementing stricter policies *(163)*. Examples might include: • requiring mandatory reporting of clinical trials, which is already a requirement in some countries, although not always effectively enforced; and • restriction of funding to sponsors and institutions that do not include verification and validation of reporting approaches as part of a trial.	The trial site Those running the trial The trial team The regulatory authority Ethics review boards Funders	–
42. Those conducting trials could report on the environmental impacts of completed trials.	Use of environmental impact assessment tools following trials, and reporting their results, can help to develop existing tools and methodologies (see consideration 6).	Those running the trial	–
43. Those conducting trials must have a travel policy that takes into account environmental considerations.	Where trials include such individuals, priority for dissemination-related travel should be given to early-career researchers, those based in LMICs or those based in low-resource settings, and for whom such travel will be valuable for their career progression.	The trial team	–

4 Climate resilience and adaptation in clinical trials

4.1 Overview

Minimal attention (in both HICs and LIMCs) has been paid to the climate resilience of clinical trials – that is, the capacity of trial systems to anticipate, respond to, cope with, recover from, and/or adapt to climate-related shocks and stress *(65)*. As the climate changes, trials are likely to become increasingly vulnerable to, for example, increased flooding or other weather events that can preclude participants and/or staff attending trial site facilities; damage to clinical trial research sites and facilities; and disruption to supply chains – and in particular cold chains – that affects the delivery of equipment and/or drugs and medications. Such current or future threats are likely to be particularly relevant to LMICs, which are disproportionately exposed to the effects of climate change because they have fewer resources to protect against them, despite their minimal contribution to historic global carbon emissions *(177)*, raising issues of justice.[21]

While "resilience" and "adaptation" are interconnected and sometimes conflated, resilience is understood as a trait or capacity, while adaptation is a process. For example, trial resilience may include, among other qualities, adaptive capacity or the ability to make adjustments – either for the future or in real time – in response to climate shocks. Trial climate adaptation will almost always include activities and initiatives that improve the resilience of a trial system.

21 Such vulnerabilities are also relevant to underserved areas of upper-middle-income countries and HICs.

While little explicit attention has been paid to trial resilience – nor indeed to health research resilience more broadly – much attention has focused on health system (and particularly health-care facility) resilience *(65)*. In fact, over 80 countries have committed to the 26th United Nations Climate Change Conference (COP26) Health Programme for climate-resilient health systems and sustainable low-carbon health systems *(178)*, including commitments to:

- conduct climate change and health vulnerability and adaptation assessments at population level and/or health-care facility level by a stated target date;
- • develop a health national adaptation plan informed by the health vulnerability and adaptation assessment, which forms part of the national adaptation plan to be published by a stated target date; and
- use the vulnerability and adaptation assessment and health national adaptation plan to facilitate access to climate change funding for health (such as project proposals submitted to the Global Environmental Facility, Green Climate Fund or Adaptation Fund or Green Climate Fund Readiness programme).

These commitments become relevant when clinical trial units are situated in health-care facilities, but beyond this, there is a need to understand issues specific to trial resilience and adaptation better. This section of the report describes:

- the vulnerabilities associated with changing climates
- the adaptations, if any, that are being (and could be) made by clinical trial actors.

It considers these within the categories of planning and governance, clinical trial facilities and infrastructure, trial participants, and supply chains and logistics.

> Trial designers should take into account geographical location and related climate vulnerability when choosing a trial site, as well as potential wider infrastructure vulnerabilities

4.2 Planning and governance

While trial resilience will benefit from national and international level adaptation measures associated with the systems within which they sit, the attribution of responsibility for implementation of trial-specific adaptation measures remains uncertain *(179)*. Needed adaptation measures include "regulatory readiness (agility)" and "regulatory flexibility" – both of which were promoted as a regulatory response to the COVID-19 pandemic. Regulatory readiness indicated the speed with which regulating bodies were able to respond to the onset of the crisis with information and guidance for clinical trialists, while regulatory flexibility indicated the scope regulating bodies provided trialists to adapt trial protocols to meet the challenges presented by the pandemic. In one example, trial regulators flexibly permitted the incorporation of decentralized elements into protocols to address trial participant and staff movement restriction *(180)*. Such flexibility was instrumental in allowing ongoing trials to continue, while protecting data integrity and participant safety *(180,181)*. Such decentralized trial methodologies also provide benefits beyond emergency situations because they help address other longstanding trial problems, such as recruitment issues *(182)*.

Furthermore, trial regulators can play a role in accounting for participant safety when participants lose trial-specific care access as a result of widespread infrastructure damage. For example, limited research on trial climate emergency response, conducted during the aftermath of Hurricane Katrina, suggests that a distinct barrier to locating and communicating with participants in the aftermath was the regulatory blocking of use of a professional investigative search service to locate participants *(183)*. Regulatory bodies can provide trialists with the regulatory flexibility not only to react to emergencies in real time – as did not happen in the Hurricane Katrina case – but also to develop innovative clinical trial methods, such as use of decentralized approaches, that can build long-term clinical trial climate resilience.

Funding bodies can play a role in beginning to build climate risk into mainstream considerations around funding policy and programming *(65,184)*. This can be achieved by incentivizing research proposals that include funds for climate adaptation strategies. However, the lack of existing literature and knowledge about clinical trials and climate adaptation suggests that much work is required before this is feasible *(184)*.

Finally, ethical review boards could possibly play a role in protecting participant safety by ensuring that clinical trials conducted in geographical locations with vulnerabilities to climate shocks are equipped with participant safety protocols in emergency situations.

Beyond top-down regulatory guidance, adaptation measures should also be addressed by clinical trial sponsors and research teams through bottom-up, facility-designed protocols; these are critical in taking context-specific action in an emergency situation *(185)*. During the COVID-19 pandemic, incorporating elements of decentralized clinical trials was explored as a means of conducting clinical trials with minimum in-person contact (*186,187)*; this is an obvious alternative to face-to-face trial conduct where needed. Decentralized trial design can also co-beneficially mitigate the environmental harms associated with trials. However, as discussed in sections 3.2 and 3.3, a pre-existing lack of digital infrastructure and digital literacy may already present a barrier to implementing decentralized trials in many LMICs (and in some regions of upper-middle-income countries and HICs), exacerbating justice issues. Furthermore, if trialists refrain from conducting trials in areas with poor digital infrastructure because of their perceived lack of ability to be adaptive, this can compound equity issues. Moreover, digital trial methodologies may also be disrupted by climate shocks, such as over-heated data centres or damage to internet fibre conduits (see section 4.3). As such, trial designers should take into account geographical location and related climate vulnerability when choosing a trial site, as well as potential wider infrastructure vulnerabilities, and should consult on any emergency protocols already in place at the location. Should emergency protocols not be in place, trial designers can increase a site's climate resilience by working with the site to introduce these protocols, thereby developing local capacity for such adaptation measures.

4.3 Clinical trial facilities and infrastructure

Depending on the type of climate shock, possible damage and/or disruption to trial research sites and the facilities they are housed in could include *(36)*:

- disrupted access to sites (after flooding or storms, for example);
- destroyed paper and/or digital records/hardware (as a result of facility damage caused by flooding or storms);
- damaged trial equipment (such as failure of ultra-low-temperature freezers or data centres following flooding or excessive heat);
- loss of biosamples (as a result of extended power loss caused by climate shocks); and
- disrupted staff working conditions (such as from excessive heat).

Climate shocks can also lead to large-scale electricity grid risk, including substation flooding and damage to

power lines during extreme cold *(188)*. Water networks and wider water quality may be affected by increased levels of sediment and pollutants due to increased precipitation and disruption to water treatment facilities during floods *(189)*, while trial site water, sanitation and hygiene facilities may also be damaged or disrupted. Finally, internet fibre conduits can be affected by rising sea levels, while local data centres can be affected by overheating – both of which can affect research facilities' ability to communicate with sponsors and research teams, as well with participants through decentralized trials (which themselves could prove to be adaptation strategies to build the climate resilience of clinical trial research sites) *(190)*. All of these can require immense financial investment to repair *(191)*. Even minor climate shock disruptions may lead to trial sites closing – disrupting trial schedules and leading to protocol deviations, and potentially invalidating trial findings *(185,192,193)*.

LMIC trial sites often display a natural resilience to difficult climatic conditions, in part owing to the principles of resourcefulness often found in these sites (see sections 3.2.1 and 3.2.2). However, while this natural resilience may help LMIC research sites cope with gradually shifting climatic conditions, such sites may still become increasingly vulnerable to climate extremes owing to the severity of potential climate shocks and the lack of resources to recover from damage to capacity. This reinforces the need to take steps to improve adaptation capacity *(194)*. Such capacity can be facilitated by clinical trial capacity development, especially when this takes into account the need for trial resilience – something that is increasingly needed, not least because climate shocks have the ability to undo any capacity development that has been achieved. For example, when considering building a new clinical trial facility, consideration should be given to its climate vulnerabilities as part of the process. Moreover, in line with the discussion in section 1.4, capacity development is best led by local, community-level actors *(195,196)*. Trial facility adaptation measures should include the following:

- Preparedness at the level of institutional leadership is vital, including awareness of the vulnerabilities of a trial research site and preparation of emergency protocols to handle future climate shocks. Conducting vulnerability and adaptation assessments for individual trial research sites can begin this process. However, the literature notes that while existing vulnerability and adaptation assessment tools can provide important checklists outlining climate vulnerabilities, they do not provide a clear path for local sites to secure funding and implement adaptation strategies *(197)*.
- Individual trial research sites should be connected to a larger subnational or national action plans for climate adaptation in health systems. Similarly, it is important for trial research sites to be connected to national-level early warning systems that can alert them to incoming extreme weather events, allowing them to implement emergency protocols in a time-sensitive fashion *(197)*.
- The trial site's material infrastructure should be checked regularly to ensure that it is maintained in line with vulnerability and adaptation assessments. This can include regular testing/checking of hazards within a site facility; a site's electricity systems and back-up power sources; its water, sanitation and hygiene, heating, ventilation and air-conditioning systems; and its physical structure to monitor identified structural damage and points that might be vulnerable during extreme weather events. Maintenance of facility access routes and potential vulnerabilities (such as trees that might block entry and exit routes if blown over or uprooted) is required. Contingency plans for cold storage unit failure; vulnerability assessments; and relocation if necessary of important equipment such as back-up power sources, physical and digital records, and digital equipment are also required.
- Staff training is essential. While many decisions regarding climate adaptation strategies take place at the leadership level of the trial site or the health-care facility in which a trial site is housed, site staff are critical to implementing many of these strategies. They must therefore be familiar with the site's vulnerabilities, educated on the threats climate shocks can pose, and aware of what plans are in place to adapt to these risks *(36,198)*. These can include staff training and education regarding the potential threats of climate shocks, effective facility management for climate resilience, and the execution of emergency protocols. They can also include regular assessments of site staff needs during shifting

weather patterns, and staff capacity – including assessments of mental strain and provision of support.
- Emergency protocols should be prepared, including plans for site evacuation; communication with study sponsor/research team/contract research organizations; recovery of samples in case of cold storage failure; and relocating key equipment and participant records where not already in place. They should also include a full set of contingency plans for management of participants (see section 4.4 for more details), emergency transportation protocols for staff, and post-disaster recovery plans for trial site material infrastructure and human resources.

Long-term adaptation planning should include the following:

- Shifting to renewable energy systems should be considered, to increase climate resilience by providing a clean, reliable back-up to sites in which grid systems are unreliable or for emergency situations, and where diesel-run generators are ineffectual due to breakdowns in the fuel supply chain. It should be noted, however, that renewable power systems may also be damaged in extreme weather events such as flooding or intense storms, depending on their location within the trial site.
- Trialists might consider shifting to paperless data management systems, such as clinical trial management systems; these provide more security for site data in cases of extreme weather events – such as flooding that can destroy paper documentation *(199)*. However, implementing clinical trial management systems comes with its own risks and barriers (see section 3.3.3).
- Deliberate long-term plans should be made for clinical trial building infrastructure – including building new clinical trial research sites with climate-resilient building materials and designs, as well as retrofitting existing clinical trial building infrastructure with extreme weather-proof materials *(36,65)*.

Some of these elements may be particularly hard to achieve – especially for under-resourced LMIC trial sites. This emphasizes the importance of capacity development to align with climate adaptation strategies, as many of these measures can be built into ongoing development efforts.

4.4 Trial participants

Clinical trial sites should have a set of contingency protocols for participant management in the event of a climate emergency (see section 4.3). These should first and foremost address participant safety (183,199). Depending on the type of emergency, these protocols should cover locating and contacting participants, and identification and meeting of participants' trial-related medical requirements.

Trial sites should ensure that participant contact information is stored in a manner that allows access in case a trial site cannot be accessed or on-site systems containing contact information have been damaged *(183)*. This should also include alternative, participant emergency contact information. Protocols around provision of the intervention to participants in emergency situations should be planned before the outset of a trial. These will be specific to the trial and the emergency. For example, flash flooding may impede access to a trial facility for a short period of time (a number of days), while a large hurricane may devastate local infrastructure, making site access impossible for the medium or long term (multiple months). Similarly, the medical needs of participants and the urgency of a response from a clinical trial team in a study testing an eczema medication differ from the needs of patients receiving interventions for critical diseases *(185)*. Clinical trial designers can take steps to ensure that, in the event a trial site is forced to close, participants still have access to their required medication. This might be by identifying alternative trial sites or health-care facilities that patients might access in case of emergency, direct delivery of drugs to patients (where possible) or provision of emergency transportation for patients in emergency situations (where possible) *(183,185,199)*.

Trialists must also reflect on participants' willingness to continue to participate in a trial. This may include utilizing elements of decentralized trials, such as facilitating short-term patient-reported outcomes, remote

patient monitoring, direct delivery of interventions or provision of emergency transportation *(183,199)*. The long-term ability to recruit trial participants may also be affected by climate change and its associated shocks, as participant populations may need to prioritize other concerns – such as finding food and shelter, looking after loved ones and local communities, energy instability, water shortages, civil unrest and so forth.

4.5 Supply chains and logistics

Trial supply chains (see section 3.1.1.4) and logistics (such as cold chains between trial facilities and central laboratories) risk being disrupted during climate shocks *(200)* which can lead to deviations in study protocols, delays in recruitment or intervention substitution. Given the geographically and organizationally diffuse nature of supply chains and related logistics, they represent a more complex vulnerability than trial facilities. A range of risks exists across various parts of these systems, all of which have the capability of disrupting the system as a whole. Specific risks include extreme heat, which can affect cold supply chains, potentially damaging investigational medicinal products. Another important risk is weather damage (such as high winds and flooding), which can affect both transportation infrastructure – preventing the movement of trial supplies and/or staff to/from facilities – and manufacturing and distribution facilities, which can disrupt entire supply chains *(201)*. In one prominent example, an extreme winter storm caused statewide blackouts in Texas, United States of America, which in turn caused the shutdown of several propylene resin manufacturing sites (202,203). As the primary material used in the manufacture of pipette tips, this resulted in a shortage of pipettes for use in the health sector.

While limited research has explored the specifics of trial supply chain and logistical vulnerability, certain adaptation strategies from the broader field of supply chain risk management are pertinent to trial actors to assess key risks.

First, risk and vulnerability assessments at every stage of a trial supply chain *(201,204,205)* can help trialists prepare contingency plans in cases of climate shocks. Given the diversity of actors involved in any given supply chain, responsibilities for this role may be problematically undefined. Industry trial actors may be better placed to conduct large-scale risk assessments, given their ability to exert control over multiple stages of a trial supply chain; they may also have significant relationships with third party suppliers. This may be more difficult for publicly funded trials, however *(205)*.

Understanding supply chain vulnerabilities can help actors diversify their choice of suppliers *(206)*, although if diversity includes non-local suppliers this may be associated with longer waiting times and/or higher prices. Further, if diversity is associated with increasing use of local suppliers, this may be difficult for LMIC-based trials because of a lack of local options. If LMIC trial sites choose to forgo using local suppliers because their manufacturing facilities are less resilient to climate shocks, this may well hamper the development of local supply chain infrastructure, or force these suppliers to charge lower prices.

Finally, shifting towards reuse, recycling and repair of trial supplies (see section 3.3.1) has co-benefits of mitigating emissions associated with trial supply chains, as well as increasing trial resilience by reducing a trial's reliance on said supply chains *(207)*. For example, reusable surgical gowns designed for use in surgical trials mean that climate shocks are less likely to disrupt trials *(208)*.

Table 4 maps specific key considerationss for climate change adaptation strategies across four elements of trial activity: planning and governance, clinical trial facilities and infrastructure, trial participants and supply chains and logistics. Note that in some trials, some actors may hold more than one responsibility.

Table 4. Study team proposals for climate change adaptation strategies

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Planning and governance			
1. Regulatory authorities should cultivate regulatory agility to enhance trial resilience.	Regulatory agility means regulatory authorities reacting quickly to climate emergencies, and providing information and guidance for clinical trialists.	The regulatory authority	–
2. Regulatory authorities should cultivate regulatory flexibility to enhance trial resilience.	Regulatory flexibility means regulatory authorities allowing trial actors the scope to adapt trial protocols to meet challenges presented by climate emergencies without fear of regulatory reprisals. Regulatory flexibility also allows trial actors to develop innovative trial methods that can help to build long-term clinical trial climate resilience.	The regulatory authority	–
3. Funding bodies should help to build climate resilience into mainstream considerations around funding.	This can be achieved by incentivizing research proposals to include funds for climate adaptation strategies. Aligning capacity development with climate adaptation, where possible, accelerates trial adaptation efforts.	Funders	The lack of existing literature and knowledge about clinical trials and climate adaptation suggests that much work will be required before this is feasible *(184)*.
4. Ethics review boards could play a role in helping to ensure the protection of participant safety in sites with climate vulnerabilities.	This can be done by ensuring that trials conducted in geographical locations with vulnerabilities to climate shocks are equipped with participant safety protocols for emergency situations.	Ethics review boards	Ethics review boards may lack resources and/or expertise in assessing environmental vulnerabilities.
5. Trial designers should consider trial climate vulnerabilities and resilient trial design.	Decentralized trial elements may be able to support trial resilience in climate emergencies where in-person site attendance might be impossible, while co-beneficially mitigating the environmental harms associated with trials. Trial designers should consider geographical location and related climate vulnerability when choosing a trial site, and should develop appropriate adaptation strategies, including emergency protocols.	Trial designers	A pre-existing lack of digital infrastructure and digital literacy already presents a barrier to implementing decentralized trials in many LMICs (and some regions of upper-middle-income countries and HICs), exacerbating justice issues. If trialists refrain from conducting trials in areas with poor digital infrastructures because of their perceived lack of climate resilience, this can compound equity issues. Digital trial methodologies may also be disrupted by climate shocks, such as over-heated data centres or damage to internet fibre conduits.

Table 4. Study team proposals for climate change adaptation strategies *(continued)*

Key cpnsideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Clinical trial facilities and infrastructure			
6. Preparedness is needed at the level of institutional leadership.	An awareness of the vulnerabilities of a trial research site and preparation of emergency protocols to handle future climate shocks is important for trial site leadership. Conducting vulnerability and adaptation assessments for individual trial research sites can begin this process.	The trial site leadership team	While vulnerability and adaptation assessment tools can provide important checklists outlining climate vulnerabilities, they do not provide a clear path for local sites to secure funding and implement adaptation strategies.
7. The trial site's material infrastructure should be checked regularly to ensure that it is maintained in line with vulnerability and adaptation assessments.	This can include regular testing/ checking of: • hazards within a site facility; • a site's electricity systems and back-up power sources; • a site's water, sanitation and hygiene systems, heating, ventilation and air-conditioning systems; • a facility's physical structure to monitor identified structural damage and points that might be vulnerable during extreme weather events; • maintenance of facility access routes and potential vulnerabilities (such as trees that might block entry and exit routes if blown over or uprooted); and • relocation, if necessary, of important equipment such as back-up power sources, physical and digital records, and digital equipment.	The trial site	Some of these considerations may be hard to effect – particularly for under-resourced LMIC trial sites. This emphasizes the importance of capacity development to align with climate adaptation strategies, as many of these measures can be built into ongoing development efforts. This barrier/opportunity applies equally to considerations 9, 10, 11 and 12 below.
8. Trial sites should be connected to larger subnational and national climate adaptation action plans.	For example, trial sites should be connected to national-level early warning systems that can alert them to incoming extreme weather events, allowing them to implement emergency protocols in a time-sensitive fashion *(197)*.	Local and national governments	This is dependent on whether subnational and national adaptation plans are in place in specific countries, which is not the case for many LMICs *(209)*. It is also dependent on whether a country has a developed a national early warning system, which is not the case for over half of the world's countries, the majority of which are LMICs *(210)*.

Table 4. Study team proposals for climate change adaptation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Clinical trial facilities and infrastructure			
9. Staff training and education on trial site climate vulnerabilities are essential.	This can include training about the potential threats of climate shocks, effective facility management for climate resilience, execution of emergency protocols and planned adaptation measures. It can also include regular assessments of site staff needs during shifting weather patterns, and staff capacity – including assessments of mental strain and provision of support.	The trial site	See consideration 7.
10. Preparation of emergency protocols	These can include, for example: • plans for site evacuation; • plans for communication with study sponsor/research team/contract research organizations; • plans for recovery of samples in case of cold storage failure; • plans for relocating key equipment and participant records where not already in place; • a full set of contingency plans for the management of participants (see below consideration 12, 13 and 14, and section 4.4 for a full description); • emergency transportation protocols for staff; and • post-disaster recovery plans for trial site material infrastructure and human resources.	The trial site Trial sponsors and designers	See consideration 7.
11. Long-term planning for trial site climate adaptation is needed.	Shifting to renewable energy systems to increase climate resilience by providing a clean, reliable back-up to sites should be considered. Shifting to paperless data management systems, such as clinical trial management systems, may also be an option. When building new clinical trial research sites, climate-resilient building materials and designs should be used. Existing trial building infrastructure should be retrofitted with extreme weather-proof materials *(65,36)*.	The trial site	Renewable power systems may also be damaged in extreme weather events such as flooding or intense storms, depending on their location within the trial site. Implementing clinical trial management systems comes with its own risks and barriers (see section 3.3.3). See also consideration 7.

Table 4. Study team proposals for climate change adaptation strategies *(continued)*

Key cpnsideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Trial participants			
12. Trial sites should have contingency protocols for locating and contacting participants.Long-term planning for trial site climate adaptation is needed.	Trial sites should ensure that participant contact information is stored in a manner that allows access in case a trial site cannot be accessed or on-site systems containing contact information have been damaged.	The trial site Trial sponsors and designers	See consideration 7.
13. Trial sites should have contingency protocols for identifying and meeting participants' trial-related medical requirements.	Protocols for provision of the intervention to participants in emergency situations should be planned before the outset of a trial, especially if adherence to medication may have a direct effect on participant health. These can include: • identifying alternative trial sites or health-care facilities that patients might access in case of emergency; • direct delivery of drugs to patients (where possible); and • provision of emergency transportation for patients in emergency situations (where possible) *(183,185,199)*.	The trial site Trial sponsors and designers	These protocols should be specific to the trial and emergency.
14. Trialists should attempt to preserve the integrity and validity of the trial, where possible.	This may include utilizing elements of decentralized trials, such as facilitating short-term patient-reported outcomes, remote patient monitoring, direct delivery of interventions or provision of emergency transportation *(183,199)*.	The trial site Trial sponsors and designers	The specific circumstances of a given climate emergency may make this impossible. Participants may be affected by climate change and its associated shocks such that participant populations need to prioritize other concerns – for example, finding food and shelter; looking after loved ones and local communities; and dealing with energy instability, water shortages, civil unrest and so forth.

Table 4. Study team proposals for climate change adaptation strategies *(continued)*

Key consideration	Sub-element	Responsibility	Open questions, further research, barriers and/or opportunities
Supply chains and logistics			
15. Risk and vulnerability assessments should be conducted at every stage of a trial supply chain to help prepare contingency plans in cases of climate shocks.	Understanding supply chain vulnerabilities can help actors diversify their choice of suppliers.	Trial sponsors and designers The trial site	Given the diversity of actors involved in any given supply chain, responsibilities for this role may be problematically undefined (except, perhaps, for large industry sponsors – see section 4.5). Even after conducting such assessments, if supplier diversity includes non-local suppliers, this may be associated with longer waiting times and/or higher prices. If LMIC trial sites choose to forgo using local suppliers because their manufacturing facilities are less resilient to climate shocks, this may well hamper the development of local supply chain infrastructure, or force these suppliers to charge lower prices *(206)*.
16. Trial supplies should be reused, recycled and repaired.	This is a co-benefit of mitigating emissions associated with trial supply chains; it also increases trial resilience, by reducing reliance on supply chains *(207)*.	Trial sponsors and designers The trial site	–

References[22]

1. What are clinical trials and studies? [website]. National Institute on Aging; 2023 (https://www.nia.nih.gov/health/clinical-trials-and-studies/what-are-clinical-trials-and-studies).
2. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research, fourth edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2013 (https://tilda.tcd.ie/epidemiology-biostatistics-course/course-material/Class2/index.php).
3. Tappin D, Sinclair L, Kee F, McFadden M, Robinson-Smith L, Mitchell A et al. Effect of financial voucher incentives provided with UK stop smoking services on the cessation of smoking in pregnant women (CPIT III): pragmatic, multicentre, single blinded, phase 3, randomised controlled trial. BMJ. 2022;379:e071522 (https://doi.org/10.1136/bmj-2022-071522).
4. Clinical trials [website]. World Health Organization; 2025 (https://www.who.int/health-topics/clinical-trials#tab=tab_1).
5. NIH clinical research trials and you: the basics [website]. National Institutes of Health; 2025 (https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics).
6. Griffiths J, Adshead F, Al-Shahi Salman R, Anderson C, Bedson E, Bliss J et al. What is the carbon footprint of academic clinical trials? A study of hotspots in 10 trials. BMJ Open. 2024;14(10):e088600 (https://doi.org/10.1136/bmjopen-2024-088600).
7. Clinical trials toolkit: routemap [website]. National Institute for Health and Care Research; 2024 (https://www.ct-toolkit.ac.uk/routemap).
8. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants [website]. World Medical Association; 2025 (https://www.wma.net/policies-post/wma-declaration-of-helsinki/).
9. ICH E6 Good clinical practice – scientific guideline [website]. European Medicines Agency; 2025 (https://www.ema.europa.eu/en/ich-e6-good-clinical-practice-scientific-guideline).
10. Number of clinical trials by year, country, WHO region and income group (1999–2024) [website]. World Health Organization; 2024 (https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-clinical-trials-by-year-country-who-region-and-income-group).
11. Heneghan C, Blacklock C, Perera R, Davis R, Banerjee A, Gill P et al. Evidence for non-communicable diseases: analysis of Cochrane reviews and randomised trials by World Bank classification. BMJ Open. 2013;3(7):e003298 (https://doi.org/10.1136/bmjopen-2013-003298).
12. The 10/90 report on health research 2001–2002. Geneva: Global Forum on Health Research; 2002 (https://www.files.ethz.ch/isn/20296/1090.02_full_text.pdf).
13. World health report 2013: research for universal health coverage. Geneva: World Health Organization; 2013 (https://iris.who.int/handle/10665/85761).
14. The route to impact [website]. European & Developing Countries Clinical Trials Partnership; 2025 https://www.edctp.org/about-us/the-route-to-impact/).
15. Franzen SRP, Chandler C, Lang T. Health research capacity development in low and middle income countries: reality or rhetoric? A systematic meta-narrative review of the qualitative literature. BMJ Open. 2017;7(1):e012332 (https://doi.org/10.1136/bmjopen-2016-012332).
16. 2024 Access to Medicine Index [website]. Access to Medicine Foundation; 2025 (https://accesstomedicinefoundation.org/sectors-and-research/index-ranking).
17. Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries – a systematic review. Int J Equity Health. 2018;17(1):37 (https://doi.org/10.1186/s12939-018-0748-6).
18. Franzen SRP, Chandler C, Siribaddana S, Atashili J, Angus B, Lang T. Strategies for developing sustainable health research capacity in low and middle-income countries: a prospective, qualitative study investigating the barriers and enablers to locally led clinical trial conduct in Ethiopia, Cameroon and Sri Lanka. BMJ Open. 2017;7(10):e017246 (https://doi.org/10.1136/bmjopen-2017-017246).

22 All references were accessed on 12 September–14 October 2025.

19. Beran D, Byass P, Gbakima A, Kahn K, Sankoh O, Tollman S et al. Research capacity building – obligations for global health partners. Lancet Glob Health. 2017;5(6):e567–8 (https://doi.org/10.1016/S2214-109X(17)30180-8).

20. Ogutu BR, Baiden R, Diallo D, Smith PG, Binka FN. Sustainable development of a GCP-compliant clinical trials platform in Africa: the Malaria Clinical Trials Alliance perspective. Malar J. 2010;9:103 (https://doi.org/10.1186/1475-2875-9-103).

21. Department for Energy Security and Net Zero. Greenhouse gas reporting: conversion factors 2023 [website]. ; 2023 (https://www.gov.uk/government/publications/greenhouse-gas-reporting-conversion-factors-2023).

22. Rau EH, Alaimo RJ, Ashbrook PC, Austin SM, Borenstein N, Evans MR et al. Minimization and management of wastes from biomedical research. Environ Health Perspect. 2000;108(Suppl 6):953–77 (https://doi.org/10.1289/ehp.00108s6953).

23. Kusturica MP, Jevtic M, Ristovski JT. Minimizing the environmental impact of unused pharmaceuticals: review focused on prevention. Front Environ Sci. 2022;10:1077974 (https://doi.org/10.3389/fenvs.2022.1077974).

24. Bailey BJ, Grupenhoff JT. Biomedical research and the environment. Environ Health Perspect. 2000;108(suppl 6):933–8 (https://doi.org/10.1289/ehp.00108s6933).

25. Tanner S. Water efficiency guide for laboratories. Washington, DC: U.S. Environmental Protection Agency (https://research-hub.nrel.gov/en/publications/water-efficiency-guide-for-laboratories/).

26. Mackillop N, Shah J, Collins M, Costelloe T, Öhman D. Carbon footprint of industry-sponsored late-stage clinical trials. BMJ Open. 2023;13(8):e072491 (https://doi.org/10.1136/bmjopen-2023-072491).

27. Sustainable Trials Study Group. Towards sustainable clinical trials. BMJ. 2007;334(7595):671–3 (https://doi.org/10.1136/bmj.39140.623137.BE).

28. Subaiya S, Hogg E, Roberts I. Reducing the environmental impact of trials: a comparison of the carbon footprint of the CRASH-1 and CRASH-2 clinical trials. Trials. 2011;12:31 (https://doi.org/10.1186/1745-6215-12-31).

29. Peired AJ, Laranjinha I, Demirtas G, Ferreira AC, Gracin S, Knoeller S et al. An urgent call for environmental accountability in nephrology clinical trials. Clin Kidney J. 2024;17(8):sfae181 (https://doi.org/10.1093/ckj/sfae181).

30. Lichter KE, Anderson J, Sim AJ, Baniel CC, Thiel CL, Chuter R et al. Transitioning to environmentally sustainable, climate-smart radiation oncology care. Int J Radiat Oncol Biol Phys. 2022;113(5):915–24 (https://doi.org/10.1016/j.ijrobp.2022.04.039).

31. Griffiths J, Fox L, Williamson PR; Low Carbon Clinical Trials Group. Quantifying the carbon footprint of clinical trials: guidance development and case studies. BMJ Open. 2024;14(1):e075755 (https://doi.org/10.1136/bmjopen-2023-075755).

32. You F, Coffey T, Powell D, Williamson PR, Gillies K. Carbon emissions associated with clinical trials: a scoping review. J Clin Epidemiol. 2025;181:111733 (https://doi.org/10.1016/j.jclinepi.2025.111733).

33. Deivanayagam TA, Osborne RE. Breaking free from tunnel vision for climate change and health. PLOS Glob Public Health. 3(3): e0001684 (https://doi.org/10.1371/journal.pgph.0001684).

34. Billiones R. Carbon footprint of clinical trials: a high-level literature review. Med Writ. 31(1):14–18 (https://journal.emwa.org/sustainable-communications/carbon-footprint-of-clinical-trials-a-high-level-literature-review/).

35. Climate change and health [website]. World Health Organization; 2025 (https://www.who.int/teams/environment-climate-change-and-health/climate-change-and-health).

36. WHO guidance for climate-resilient and environmentally sustainable health care facilities. Geneva: World Health Organization; 2020 (https://iris.who.int/handle/10665/335909). Licence: CC BY-NC-SA 3.0 IGO.

37. Procurement: guiding principles [website]. World Health Organization; 2025 (https://www.who.int/about/accountability/procurement/principles-and-processes/guiding-principles).

38. Samuel G. Responsibility for the environmental impact of data-intensive research: an exploration of UK health researchers. Sci Eng Ethics. 2024;30(4):33 (https://doi.org/10.1007/s11948-024-00495-z).

39. Samuel G. UK health researchers' considerations of the environmental impacts of their data-intensive practices and its relevance to health inequities. BMC Med Ethics. 2023;24(1):90 (https://doi.org/10.1186/s12910-023-00973-2).

40. Potter VR, Potter L. Global bioethics: converting sustainable development to global survival. Med Glob Surviv. 1995;2(3):185–91 (https://doi.org/10.1080/11287462.2001.10800809).

41. Odero B, Nderitu D, Samuel G. The Ubuntu way: ensuring ethical AI integration in health research. Wellcome Open Res. 2024;9:62 (https://doi.org/10.12688/wellcomeopenres.23021.1).

42. The Lancet Public Health. No public health without planetary health. Lancet Public Health. 2022;7(4):e291 (https://doi.org/10.1016/S2468-2667(22)00068-8).

43. Inglis JT, editor. Traditional ecological knowledge: concepts and cases. Ottawa: International Program on Traditional Ecological Knowledge International Development Research Centre; 1993 (https://idrc-crdi.ca/en/book/traditional-ecological-knowledge-concepts-and-cases).

44. Mies M, Shiva V. Ecofeminism. Halifax, NS: Fernwood Publishing; 1993 (https://fernwoodpublishing.ca/book/ecofeminism).

45. Rawbone R. Principles of biomedical ethics, 7th edition. Occup Med. 2015;65(1):88–9 (https://doi.org/10.1093/occmed/kqu158).

46. Samuel G, Hardcastle F, Lucassen AM. Environmental sustainability and biobanking: a pilot study of the field. New Genet Soc. 2022;41(2):157–75 (https://doi.org/10.1080/14636778.2022.2093707).

47. Pierce J, Jameton A. The ethics of environmentally responsible health care. Oxford: Oxford University Press; 2004 (https://global.oup.com/academic/product/the-ethics-of-environmentally-responsible-health-care-9780195139037).

48. D'Souza J, Samuel G. Clinical research risks, climate change, and human health. JAMA. 2023;330(23):2247–8 (https://doi.org/10.1001/jama.2023.23724).

49. Samuel G, Richie C. Reimagining research ethics to include environmental sustainability: a principled approach, including a case study of data-driven health research. J Med Ethics. 2023;49(6):428–33 (https://doi.org/10.1136/jme-2022-108489).

50. Young IM. Responsibility for justice. Oxford: Oxford University Press; 2011 (https://academic.oup.com/book/4381).

51. Fraser N. Abnormal justice. Crit Inq. 2008;34(3):393–422 (https://doi.org/10.1086/589478).

52. Environmental and social safeguards framework, first edition. Geneva: World Health Organization; 2024 (https://www.who.int/publications/m/item/who-environmental-and-social-safeguards-framework). Licence: CC BY-NC-SA 3.0 IGO.

53. Galvin R, Harris JR. Individual moral responsibility and the problem of climate change. Anal Krit. 2014;36(2):383–96 (https://doi.org/10.1515/auk-2014-0210).

54. Jamieson D. Responsibility and climate change. Global Justice: Theory Practice Rhetoric. 2015;8(2):23–42 (https://doi.org/10.21248/gjn.8.2.86).

55. Schinkel A. Causal and moral responsibility of individuals for (the harmful consequences of) climate change. Ethics, Policy Environ. 2011;14(1):35–7 (https://doi.org/10.1080/21550085.2011.561592).

56. Douglas HE. The moral responsibilities of scientists (tensions between autonomy and responsibility). Am Philos Q. 2003;40(1):59–68 (http://www.jstor.org/stable/20010097).

57. Haraway DJ. Staying with the trouble: making kin in the Chthulucene. Durham, NC: Duke University Press; 2016 (https://www.dukeupress.edu/staying-with-the-trouble).

58. Samuel G, Williamson P, Fox L, Graham M. Understanding current thinking around carbon emission impact assessment and clinical trials regulation. Liverpool: MRC-NIHR Trials Methodology Research Partnership; 2025 (https://www.methodologyhubs.mrc.ac.uk/about/working-groups/trial-conductwg/tcwg-subgroup-greener-trials/enabling-lower-carbon-clinical-trials-cict-project/).

59. FDA takes additional steps to advance decentralized clinical trials [news release]. U.S. Food and Drug Administration; 2 May 2023 (https://www.fda.gov/news-events/press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials).

60. Facilitating decentralised clinical trials in the EU [news release]. European Medicines Agency; 19 December 2022 (https://www.ema.europa.eu/en/news/facilitating-decentralised-clinical-trials-eu).

61. Van Norman GA. Decentralized clinical trials: the future of medical product development? J Am Coll Cardiol Basic Trans Science. 2021;6(4):384–7 (https://doi.org/10.1016/j.jacbts.2021.01.011).

62. Aiyegbusi OL, Cruz Rivera S, Kamudoni P, Anderson N, Collis P, Denniston AK et al. Recommendations to promote equity, diversity and inclusion in decentralized clinical trials. Nat Med. 2024;30(11):3075–84 (https://doi.org/10.1038/s41591-024-03323-w).

63. Vayena E, Blasimme A, Sugarman J. Decentralised clinical trials: ethical opportunities and challenges. Lancet Digit Health. 2023;5(6):e390–4 (https://doi.org/10.1016/S2589-7500(23)00052-3).

64. Sommer C, Zuccolin D, Arnera V, Schmitz N, Adolfsson P, Colombo N et al. Building clinical trials around patients: evaluation and comparison of decentralized and conventional site models in patients with low back pain. Contemp Clin Trials Commun. 2018;11:120–6 (https://doi.org/10.1016/j.conctc.2018.06.008).

65. Operational framework for building climate resilient health systems. Geneva: World Health Organization; 2015 (https://iris.who.int/handle/10665/189951).

66. Glossary. In: Pachauri RK, Meyer LA, editors. Climate change 2014: synthesis report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Geneva: Intergovernmental Panel on Climate Change; 2014 (https://www.ipcc.ch/report/ar5/syr/).

67. Jones MW, Peters GP, Gasser T, Andrew RM, Schwingshackl C, Gütschow J et al. National contributions to climate change due to historical emissions of carbon dioxide, methane, and nitrous oxide since 1850. Sci Data. 2023;10(1):155 (https://doi.org/10.1038/s41597-023-02041-1).

68. Chancel L, Bothe P, Voituriez T. Climate inequality report 2023. Paris: World Inequality Lab; 2023 (https://wid.world/news-article/climate-inequality-report-2023-fair-taxes-for-a-sustainable-future-in-the-global-south/).

69. MRC-NIHR Trials Methodology Research Partnership (TMRP) [website]. MRC-NIHR Trials Methodology Research Partnership; 2025 (https://www.methodologyhubs.mrc.ac.uk/about/tmrp).

70. WHO recommends injectable lenacapavir for HIV prevention [news release]. World Health Organization; 14 July 2025 (https://www.who.int/news/item/14-07-2025-who-recommends-injectable-lenacapavir-for-hiv-prevention).

71. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet. 2009374(9683):86–9 (https://doi.org/10.1016/S0140-6736(09)60329-9).

72. Kim D, Hasford J. Redundant trials can be prevented, if the EU clinical trial regulation is applied duly. BMC Med Ethics. 2020;21(1):107 (https://doi.org/10.1186/s12910-020-00536-9).

73. Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. Lancet. 2010;376(9734):20–1 (https://doi.org/10.1016/S0140-6736(10)61045-8).

74. Gillies K, Chalmers I, Glasziou P, Elbourne D, Elliott J, Treweek S. Reducing research waste by promoting informed responses to invitations to participate in clinical trials. Trials. 2019;20(1):613 (https://doi.org/10.1186/s13063-019-3704-x).

75. Fandino W. Formulating a good research question: pearls and pitfalls. Indian J Anaesth. 2019;63(8):611–16 (https://doi.org/10.4103/ija.IJA_198_19).

76. Guidance for best practices for clinical trials. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/378782). Licence: CC BY-NC-SA 3.0 IGO.

77. Ioannidis JP. Clinical trials: what a waste. BMJ. 2014;349:g7089 (https://doi.org/10.1136/bmj.g7089).

78. Yordanov Y, Dechartres A, Porcher R, Boutron I, Altman DG, Ravaud P. Avoidable waste of research related to inadequate methods in clinical trials. BMJ. 2015;350:h809 (https://doi.org/10.1136/bmj.h809).

79. Greg Miller W, Myers GL, Lou Gantzer M, Kahn SE, Schönbrunner ER, Thienpont LM et al. Roadmap for harmonization of clinical laboratory measurement procedures. Clin Chem. 2011;57(8):1108–17 (https://doi.org/10.1373/clinchem.2011.164012).

80. Costa LJ, Derman BA, Bal S, Sidana S, Chhabra S, Silbermann R et al. International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. Leukemia. 2021;35(1):18–30 (https://doi.org/10.1038/s41375-020-01012-4).

81. A framework for change [website]. Sustainable Healthcare Coalition; 2025 (https://shcoalition.org/clinical-trial-carbon-calculator-beta-test/).

82. Pathmanathan P, Aycock K, Badal A, Bighamian R, Bodner J, Craven BA et al. Credibility assessment of in silico clinical trials for medical devices. PLoS Comput Biol. 2024;20(8):e1012289 (https://doi.org/10.1371/journal.pcbi.1012289).

83. Saluja T, Giri BR, Chaudhary S, Tamrakar D, Kanodia P, Palkar S et al. Challenges and opportunities in setting up a phase III vaccine clinical trial in resource limited settings: experience from Nepal. Hum Vaccin Immunother. 2021;17(7):2149–57 (https://doi.org/10.1080/21645515.2020.1855955).

84. Ali R, Finlayson A, INDOX Cancer Research Network. Building capacity for clinical research in developing countries: the INDOX Cancer Research Network experience. Glob Health Action. 2012:5 (https://doi.org/10.3402/gha.v5i0.17288).

85. Aliyu MH, Sani MU, Ingles DJ, Tsiga-Ahmed FI, Musa BM, Audet CM et al. The V-BRCH Project: building clinical trial research capacity for HIV and noncommunicable diseases in Nigeria. Health Res Policy Syst. 2021;19(1):32 (https://doi.org/10.1186/s12961-020-00656-z).

86. Building climate-resilient, sustainable, and low-carbon health supply chains: key priorities for collective action. Geneva: Unitaid; 2025 (https://unitaid.org/publication/building-climate-resilient-sustainable-and-low-carbon-health-supply-chains-key-priorities-for-collective-action/).

87. Beg S, Handa M, Shukla R, Rahman M, Almalki WH, Afzal O et al. Wearable smart devices in cancer diagnosis and remote clinical trial monitoring: transforming the healthcare applications. Drug Discov Today. 2022;27(10):103314 (https://doi.org/10.1016/j.drudis.2022.06.014).

88. Rizan C, Mortimer F, Stancliffe R, Bhutta MF. Plastics in healthcare: time for a re-evaluation. J R Soc Med. 2020;113(2):49–53 (https://doi.org/10.1177/0141076819890554).

89. Greene J, Skolnik CL, Merritt MW. How medicine becomes trash: disposability in health care. Lancet. 2022;400(10360):P1298–9 (https://doi.org/10.1016/S0140-6736(22)01941-9).

90. Nielsen TD, Hasselbach J, Holmberg K, Stripple J. Politics and the plastic crisis: a review throughout the plastic life cycle. WIREs Energy Environ. 2020;9(1):e360 (https://doi.org/10.1002/wene.360).

91. MacLeod M, Arp HPH, Tekman MB, Jahnke A. The global threat from plastic pollution. Science. 2021;373(6550):61–5 (https://doi.org/10.1126/science.abg5433).

92. Greener Pharmaceuticals' Regulatory Highway: call for action on regulatory support for introduction of more sustainable products and services. Geneva: World Health Organization; 2024 (https://www.who.int/publications/m/item/greener-pharmaceuticals-regulatory-highway).

93. Djurisic S, Rath A, Gaber S, Garattini S, Bertele V, Ngwabyt SN et al. Barriers to the conduct of randomised clinical trials within all disease areas. Trials. 2017;18(1):360 (https://doi.org/10.1186/s13063-017-2099-9).

94. Khadem Broojerdi A, Baran Sillo H, Ostad Ali Dehaghi R, Ward M, Refaat M, Parry J. The World Health Organization Global Benchmarking Tool: an instrument to strengthen medical products regulation and promote universal health coverage. Front Med (Lausanne). 2020;7:457 (https://doi.org/10.3389/fmed.2020.00457).

95. Six-month update: EvolveBBMRI's progress in datafication, greening biobanks, and One Health integration [website]. Biobanking and BioMolecular resources Research Infrastructure – European Research Infrastructure Consortium; 2025 (https://www.bbmri-eric.eu/news-events/evolve-bbmri-six-month-update/).

96. Samuel G, Lucivero F, Lucassen AM. Sustainable biobanks: a case study for a green global bioethics. Glob Bioeth. 2022;33(1):50–64 (https://doi.org/10.1080/11287462.2021).

97. Siena LM, Papamanolis L, Siebert MJ, Bellomo RK, Ioannidis JPA. Industry involvement and transparency in the most cited clinical trials, 2019–2022. JAMA Netw Open. 2023;6(11):e2343425 (https://doi.org/10.1001/jamanetworkopen.2023.43425).

98. MacFarlane M, Samuel G. (2022). Addressing the environmental impact of (digital) health research: conversations with UK funders – summary report. London: King's College London; 2022 (https://kclpure.kcl.ac.uk/portal/en/publications/addressing-the-environmental-impact-of-digital-health-research-co).

99. Enabling greener biomedical research: FORUM workshop on Wednesday 15 March 2023. London: Academy of Medical Sciences; 2023 (https://acmedsci.ac.uk/next-gen-researchers-exploring-climate-health).

100. Environmental sustainability funding policy [website]. Wellcome Trust; 2025 (https://wellcome.org/grant-funding/guidance/policies-grant-conditions/environmental-sustainability-policy).

101. Heidelberg Agreement on Environmental Sustainability in Research Funding [website]. Federation of European Biochemical Societies; 2025 (https://network.febs.org/posts/heidelberg-agreement-on-environmental-sustainability-in-research-funding).

102. Gamble C, Dudley L, Allam A, Bell P, Goodare H, Hanley B et al. Patient and public involvement in the early stages of clinical trial development: a systematic cohort investigation. BMJ Open. 2014;4(7):e005234 (https://doi.org/10.1136/bmjopen-2014-005234).

103. Concordat for the Environmental Sustainability of Research and Innovation Practice [website]. Wellcome Trust; 2025 (https://wellcome.org/about-us/positions-and-statements/environmental-sustainability-concordat).

104. Li G, Wu Q, Jin Y, Vanniyasingam T, Thabane L. Key factors of clinical research network capacity building. J Venom Anim Toxins Incl Trop Dis. 2018;24:15 (https://doi.org/10.1186/s40409-018-0152-0).

105. Gilbert SG. Supplementing the traditional institutional review board with an environmental health and community review board. Environ Health Perspect. 2006;114(10):1626–9 (https://doi.org/10.1289/ehp.9005).

106. Hyder AA, Rattani A, Pratt B. Research capacity strengthening in low- and middle-income countries: ethical explorations. J Law Med Ethics. 2017;45(1):129–37 (https://doi.org/10.1177/1073110517703106).

107. Reddy B, Thomas S, Karachiwala B, Sadhu R, Iyer A, Sen G et al. A scoping review of the impact of organisational factors on providers and related interventions in LMICs: implications for respectful maternity care. PLOS Glob Public Health. 2022;2(10):e0001134 (https://doi.org/10.1371/journal.pgph.0001134).

108. Novak M, Drummond K, Kumar A. Healthcare professionals' experiences with education in short term medical missions: an inductive thematic analysis. BMC Public Health. 2022;22(1):997 (https://doi.org/10.1186/s12889-022-13349-9).

109. Khogali A, Ahmed A, Ibrahim M, Karrar K, Elsheikh M, Abdelraheem E et al. Building power-ful health systems: the impacts of electrification on health outcomes in LMICs. Psychol Health Med. 2022;27(Supp1):124–37 (https://doi.org/10.1080/13548506.2022.2109049).

110. Franco A, Shaker M, Kalubi D, Hostettler S. A review of sustainable energy access and technologies for healthcare facilities in the Global South. Sustain Energy Technol Assess. 2017:92–105 (https://doi.org/10.1016/j.seta.2017.02.022).

111. Crocker JC, Ricci-Cabello I, Parker A, Hirst JA, Chant A, Petit-Zeman S et al. Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis. BMJ. 2018;363:k4738 (https://doi.org/10.1136/bmj.k4738).

112. Kadam RA, Borde SU, Madas SA, Salvi SS, Limaye SS. Challenges in recruitment and retention of clinical trial subjects. Perspect Clin Res. 2016;7(3):137–43 (https://doi.org/10.4103/2229-3485.184820).

113. Chaudhari N, Ravi R, Gogtay NJ, Thatte UM. Recruitment and retention of the participants in clinical trials: challenges and solutions. Perspect Clin Res. 2020;11(2):64–9 (https://doi.org/10.4103/picr.PICR_206_19).

114. Bagley HJ, Short H, Harman NL, Hickey HR, Gamble CL, Woolfall K et5 al. A patient and public involvement (PPI) toolkit for meaningful and flexible involvement in clinical trials – a work in progress. Res Involv Engagem. 2016;2:15 (https://doi.org/10.1186/s40900-016-0029-8).

115. Davies GR, Phillips PP, Jaki T. Adaptive clinical trials in tuberculosis: applications, challenges and solutions. Int J Tuberc Lung Dis. 2015;19(6):626–34 (https://doi.org/10.5588/ijtld.14.0988).

116. Tirupakuzhi Vijayaraghavan BK, Gupta E, Ramakrishnan N, Beane A, Haniffa R, Lone N et al. Barriers and facilitators to the conduct of critical care research in low and lower-middle income countries: a scoping review. PLoS One. 2022;17(5):e0266836 (https://doi.org/10.1371/journal.pone.0266836).

117. Ye J, Xiong S, Wang T, Li J, Cheng N, Tian M, Yang Y. The roles of electronic health records for clinical trials in low- and middle-income countries: scoping review. JMIR Med Inform. 2023;11:e47052 (https://doi.org/10.2196/47052).

118. Kwon C, Essayei L, Spencer M, Etheridge T, Venkatesh R, Vengadesan N et al. The environmental impacts of electronic medical records versus paper records at a large eye hospital in India: life cycle assessment study. J Med Internet Res. 2024;26:e42140 (https://doi.org/10.2196/42140).

119. Fougerou-Leurent C, Forteau L, Perrot-Loyer M, Renault A, Mouchel C, Rousseau C et al. Evaluating the environmental impact of clinical research: a life-cycle analysis of a French academic randomised clinical trial. medRxiv 2024;24316343 [pre-print before peer review] (https://doi.org/10.1101/2024.10.29.24316343).

120. Vayena E, Blasimme A, Sugarman J. Decentralised clinical trials: ethical opportunities and challenges. Lancet Digit Health. 2023;5(6):e390–4 (https://doi.org/10.1016/S2589-7500(23)00052-3).

121. Rogers A, De Paoli G, Subbarayan S, Copland R, Harwood K, Coyle J et al. A systematic review of methods used to conduct decentralised clinical trials. Br J Clin Pharmacol. 2022;88(6):2843–62 (https://doi.org/10.1111/bcp.15205).

122. Kohl SH, Schmidt-Lucke C. Clinical trials to go green – a sustainable argument for decentralised digital clinical trials. Imaging Neurosci (Camb). 2023;1:imag-1-00014 (https://doi.org/10.1162/imag_a_00014).

123. Hui CY, Abdulla A, Ahmed Z, Goel H, Monsur Habib GM, Teck Hock T et al. Mapping national information and communication technology (ICT) infrastructure to the requirements of potential digital health interventions in low- and middle-income countries. J Glob Health. 2022;12:04094 (https://doi.org/10.7189/jogh.12.04094).

124. Khozin S, Coravos A. Decentralized trials in the age of real-world evidence and inclusivity in clinical investigations. Clin Pharmacol Ther. 2019;106(1):25–7 (https://doi.org/10.1002/cpt.1441).

125. Cosoli G, Spinsante S, Scalise L. Wrist-worn and chest-strap wearable devices: systematic review on accuracy and metrological characteristics. Measurement. 2020;159:107789 (https://doi.org/10.1016/j.measurement.2020.107789).

126. Lippi G, Salvagno GL, Montagnana M, Franchini M, Guidi GC. Phlebotomy issues and quality improvement in results of laboratory testing. Clin Lab. 2006;52(56):217–30.

127. Berthon-Jones N, Courtney-Vega K, Donaldson A, Haskelberg H, Emery S, Puls R. Assessing site performance in the Altair study, a multinational clinical trial. Trials. 2015;16:138 (https://doi.org/10.1186/s13063-015-0653-x).

128. Dale JC, Ruby SG. Specimen collection volumes for laboratory tests: a College of American Pathologists study of 140 laboratories. Arch Pathol Lab Med. 2003;127(2):162–8 (https://doi.org/10.5858/2003-127-162-SCVFL).

129. Grizzle WE, Sexton KC. Commentary on improving biospecimen utilization by classic biobanks: identifying past and minimizing future mistakes. Biopreserv Biobank. 2019;17(3):243–7 (https://doi.org/10.1089/bio.2018.0080).

130. Graham M, Samuel G, Farley M. Roadmap for low-carbon ultra-low temperature storage in biobanking. J Transl Med. 2024;22(1):747 (https://doi.org/10.1186/s12967-024-05383-5).

131. Legett R. Field demonstration of high-efficiency ultra-low-temperature laboratory freezers. Washington, DC: U.S. Department of Energy; 2014 (https://www.energy.gov/sites/prod/files/2014/11/f19/ult_demo_report.pdf).

132. Farley M, McTeir B, Arnott A, Evans A. Efficient ULT freezer storage: an Investigation of ULT freezer energy and temperature dynamics. Edinburgh: University of Edinburgh; 2015 (https://edwebcontent.ed.ac.uk/sites/default/files/atoms/files/efficient_ult_freezer_storage.pdf).

133. Benton K, Yang X, Wang Z. Life cycle energy assessment of a standby diesel generator set. J Clean Prod. 2017;149:265–74 (https://doi.org/10.1016/j.jclepro.2017.02.082).

134. Tassou SA, De-Lille G, Ge YT. Food transport refrigeration – approaches to reduce energy consumption and environmental impacts of road transport. Appl Therm Eng. 2009;29(8–9):1467–77 (https://doi.org/10.1016/j.applthermaleng.2008.06.027).

135. Sustainable cooling and cold chain solutions: an Official Development Assistance business case. London: Department for Environment, Food and Rural Affairs; 2024 (https://devtracker.fcdo.gov.uk/programme/GB-GOV-7-32CPL-00499-KA/documents).

136. De Boeck K, Decouttere C, Vandaele N. Vaccine distribution chains in low- and middle-income countries: a literature review. Omega. 2020;97:102097 (https://doi.org/10.1016/j.omega.2019.08.004).

137. Rising cost of gas to blame for dry ice shortages in UK and Europe [news release]. Manufacturing Chemist; 14 September 2022 (https://manufacturingchemist.com/rising-cost-of-gas-to-blame-for-dry-ice-shortages-in-uk-and-europe-203555).

138. Olsen R, Bihlet AR, Kalakou F, Andersen JR. The impact of clinical trial monitoring approaches on data integrity and cost – a review of current literature. Eur J Clin Pharmacol. 2016;72(4):399–412 (https://doi.org/10.1007/s00228-015-2004-y).

139. Venet D, Doffagne E, Burzykowski T, Beckers F, Tellier Y, Genevois-Marlin E et al. A statistical approach to central monitoring of data quality in clinical trials. Clin Trials. 2012;9(6):705–13 (https://doi.org/10.1177/1740774512447898).

140. Bakobaki JM, Rauchenberger M, Joffe N, McCormack S, Stenning S, Meredith S. The potential for central monitoring techniques to replace on-site monitoring: findings from an international multi-centre clinical trial. Clin Trials. 2012;9(2):257–64 (https://doi.org/10.1177/1740774511427325).

141. Buyse M. Centralized statistical monitoring as a way to improve the quality of clinical data [news release]. Applied Clinical Trials; 24 March 214 (https://www.appliedclinicaltrialsonline.com/view/centralized-statistical-monitoring-way-improve-quality-clinical-data).

142. Berkhout F, Hertin J. De-materialising and re-materialising: digital technologies and the environment. Futures. 2004;36(8):903–20 (https://doi.org/10.1016/j.futures.2004.01.003).

143. Lannelongue L, Grealey J, Inouye M. Green algorithms: quantifying the carbon footprint of computation. Adv Sci (Weinh). 2021;8(12):2100707 (https://doi.org/10.1002/advs.202100707).

144. Sheetz N, Wilson B, Benedict J, Huffman E, Lawton A, Travers M et al. Evaluating source data verification as a quality control measure in clinical trials. Ther Innov Regul Sci. 2014;48(6):671–80 (https://doi.org/10.1177/2168479014554400).

145. Pogue JM, Devereaux PJ, Thorlund K, Yusuf S. Central statistical monitoring: detecting fraud in clinical trials. Clin Trials. 2013;10(2):225–35 (https://doi.org/10.1177/1740774512469312).

146. McHugh CG, Gottreich JR, Kumara MT, Selzer F, Collins JE, Losina et al. An approach to virtual clinical trial site visits: lessons from the MeTeOR trial. Osteoarthr Cartil Open. 2023;5(1):100337 (https://doi.org/10.1016/j.ocarto.2023.100337).

147. Godfrey C, Tauscher G, Hunsberger S, Austin M, Scott L, Schouten JT et al. A survey of tuberculosis infection control practices at the NIH/NIAID/DAIDS-supported clinical trial sites in low and middle income countries. BMC Infect Dis. 2016;16:269 (https://doi.org/10.1186/s12879-016-1579-y).

148. Modlin CE, Kankaka EN, Chang LW, Sewankambo NK, Ali J. Exploring HIV/AIDS investigator perceptions of equity within research partnerships between low-and middle-income and high-income countries: a pilot survey. Health Res Policy Syst. 2023;21(1):32 (https://doi.org/10.1186/s12961-023-00977-9).

149. Wang L, Motti EF. The increasing shift of clinical trials to CROs. Pharm Outsourcing. 2015;16(3):174597 (https://www.pharmoutsourcing.com/Featured-Articles/174597-The-Increasing-Shift-of-Clinical-Trials-to-CROs/).

150. Miller MI, Shih LC, Kolachalama VB. Machine learning in clinical trials: a primer with applications to neurology. Neurotherapeutics. 2023;20(4):1066–80 (https://doi.org/10.1007/s13311-023-01384-2).

151. Weissler EH, Naumann T, Andersson T, Ranganath R, Elemento O, Luo Y et al. The role of machine learning in clinical research: transforming the future of evidence generation. Trials. 2021;22(1):537 (https://doi.org/10.1186/s13063-021-05489-x).

152. FAIR principles [website]. GO FAIR; 2025 (https://www.go-fair.org/fair-principles/).

153. Hey SP, Dellapina M, Lindquist K, Hartog B, LaRoche J. Digital health technologies in clinical trials: an ontology-driven analysis to inform digital sustainability policies. Ther Innov Regul Sci. 2023;57(6):1269–78 (https://doi.org/10.1007/s43441-023-00560-y).

154. Malkin R, Keane A. Evidence-based approach to the maintenance of laboratory and medical equipment in resource-poor settings. Med Biol Eng Comput. 2010;48(7):721–6 (https://doi.org/10.1007/s11517-010-0630-1).

155. Rush A, Byrne JA, Watson PH. Applying findable, accessible, interoperable, and reusable principles to biospecimens and biobanks. Biopreserv Biobank. 2024;22(6):550–6 (https://doi.org/10.1089/bio.2023.0110).

156. Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic). Amsterdam: European Medicines Agency; 2018 (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-and-archiving-clinical-trial-master-file-paper-andor-electronic_en.pdf).

157. Amberber M, Addis Y. Paper burning and associated pollution problems in higher educational institutions of Ethiopia: the need and potential for recycling. Int J Waste Resour. 2017;7(3):1000290 (https://doi.org/10.4172/2252-5211.1000290).

158. Rosa C, Marsch LA, Winstanley EL, Brunner M, Campbell ANC. Using digital technologies in clinical trials: current and future applications. Contemp Clin Trials. 2021;100:106219 (https://doi.org/10.1016/j.cct.2020.106219).

159. Mealer M, Kittelson J, Thompson BT, Wheeler AP, Magee JC, Sokol RJ et al. Remote source document verification in two national clinical trials networks: a pilot study. PLoS One. 2013;8(12):e81890 (https://doi.org/10.1371/journal.pone.0081890).

160. Gupta SK. Paperless clinical trials: myth or reality? Indian J Pharmacol. 2015;47(4):349–53 (https://doi.org/10.4103/0253-7613.161247).

161. Kumar P, Sammut SM, Madan JJ, Bucher S, Kumar MB. Digital ≠ paperless: novel interfaces needed to address global health challenges. BMJ Glob Health. 2021;6(4):e005780 (https://doi.org/10.1136/bmjgh-2021-005780).

162. SPIRIT–CONSORT [website]. University of Oxford; 2025 (https://www.consort-spirit.org/).

163. Zarin DA, Goodman SN, Kimmelman J. Harms from uninformative clinical trials. JAMA. 2019;322(9):813–14 (https://doi.org/10.1001/jama.2019.9892).

164. Chan AW, Song F, Vickers A, Jefferson T, Dickersin K, Gøtzsche PC et al. Increasing value and reducing waste: addressing inaccessible research. Lancet. 2014;383(9913):257–66 (https://doi.org/10.1016/S0140-6736(13)62296-5).

165. Gøtzsche PC. Why we need easy access to all data from all clinical trials and how to accomplish it. Trials. 2011;12:249 (https://doi.org/10.1186/1745-6215-12-249).

166. Pirosca S, Shiely F, Clarke M, Treweek S. Tolerating bad health research: the continuing scandal. Trials. 2022;23(1):458 (https://doi.org/10.1186/s13063-022-06415-5).

167. Al-Shahi Salman R, Beller E, Kagan J, Hemminki E, Phillips RS, Savulescu J et al. Increasing value and reducing waste in biomedical research regulation and management. Lancet. 2014;383(9912):176–85 (https://doi.org/10.1016/S0140-6736(13)62297-7).

168. Hamilton F, Arnold D, Lilford R. Bad research is not all bad. Trials. 2023;24:680 (https://doi.org/10.1186/s13063-023-07706-1).

169. Examples of COVID-19 research within TMRP [website]. Medical Research Council; 2025 (https://www.methodologyhubs.mrc.ac.uk/about/tmrpcovid/).

170. Petersen JJ, Hemberg L, Thabane L, Hopewell S, Chan AW, Hróbjartsson A et al. Integrating environmental outcomes in randomised clinical trials: a call to action. Lancet. 2025;405(10477):446–8 (https://doi.org/10.1016/S0140-6736(24)02666-7).

171. DiGiulio S. Streamlining regulatory requirements to decentralize cancer clinical trials. Oncol Times. 2025;47(1)31 (https://doi.org/10.1097/01.COT.0001097284.71153.bd).

172. Harvey RD, Miller TM, Hurley PA, Thota R, Black LJ, Bruinooge SS et al. A call to action to advance patient-focused and decentralized clinical trials. Cancer. 2024;130(8):1193–203 (https://doi.org/10.1002/cncr.35145).

173. Singh R, Wang W, Chakravarty A, Wang J, Uyama Y. Simultaneous global drug development and multiregional clinical trials (MRCT): 5 years after implementation of ICH E17 guidelines. Ther Innov Regul Sci. 2024;58(5):845–54 (https://doi.org/10.1007/s43441-024-00639-0).

174. Sabo JA. To ensure innovation in clinical trials, the rules need to change [blog]. In: Health Affairs Forefront; 12 June 2024 (https://www.healthaffairs.org/content/forefront/ensure-innovation-clinical-trials-rules-need-change).

175. Bendiscioli S. Heidelberg Agreement on Environmental Sustainability in Research Funding [blog]. In: Viewpoints; 25 October 2024 (https://network.febs.org/posts/heidelberg-agreement-on-environmental-sustainability-in-research-funding).

176. Core Outcome Measures in Effectiveness Trials [website]. COMET Initiative; 2025 (https://www.comet-initiative.org/).

177. Evans S. Analysis: Which countries are historically responsible for climate change? [blog] In: CarbonBrief; 5 October 2021 (https://www.carbonbrief.org/analysis-which-countries-are-historically-responsible-for-climate-change/).

178. Alliance for Transformative Action on Climate and Health (ATACH) [website]. World Health Organization; 2025 (https://www.who.int/initiatives/alliance-for-transformative-action-on-climate-and-health/cop26-health-programme).

179. Mees HLP, Driessen PPJ, Runhaar HAC. Exploring the scope of public and private responsibilities for climate adaptation. J Envir Pol Plan. 2012;14(3):305–30 (https://doi.org/10.1080/1523908X.2012.707407).

180. de Jong AJ, Santa-Ana-Tellez Y, van Thiel GJMW, Zuidgeest MGP, Siiskonen SJ, Mistry D et al. COVID-19 and the emerging regulatory guidance for ongoing clinical trials in the European Union. Clin Pharmacol Ther. 2021;109(6):1517–27 (https://doi.org/10.1002/cpt.2225).

181. Bolislis WR, de Lucia ML, Dolz F, Mo R, Nagaoka M, Rodriguez H et al. Regulatory agilities in the time of COVID-19: overview, trends, and opportunities. Clin Ther. 2021;43(1):124–39 (https://doi.org/10.1016/j.clinthera.2020.11.015).

182. de Jong AJ, Zuidgeest MGP, Santa-Ana-Tellez Y, de Boer A, Gardarsdottir H; Trials@Home Consortium. Regulatory readiness to facilitate the appropriate use of innovation in clinical trials: the case of decentralized clinical trial approaches. Drug Discov Today. 2024;29(11):104180 (https://doi.org/10.1016/j.drudis.2024.104180).

183. McDuffie R, Summerson J, Reilly P, Blackwell C, Goff D, Kimel AR et al. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Hurricane Katrina: lessons for managing clinical trials during and after a natural disaster. Contemp Clin Trials. 2008;29(5):756–61 (https://doi.org/10.1016/j.cct.2008.05.006).

184. Tye S. Mainstreaming climate adaptation planning and action into health systems in Fiji, Ghana, and Benin. Washington, DC: World Resources Institute; 2021 (https://doi.org/10.46830/wriwp.19.00119).

185. Lunt H, Heenan H. Mitigating the impact of disasters and emergencies on clinical trials site conduct: a site perspective following major and minor unforeseen events. Contemp Clin Trials Commun. 2019;16:100487 (https://doi.org/10.1016/j.conctc.2019.100487).

186. Banks MA. Core concept: in the wake of COVID-19, decentralized clinical trials move to center stage. Proc Natl Acad Sci U S A. 2021;118(47):e2119097118 (https://doi.org/10.1073/pnas.2119097118).

187. Dorsey ER, Kluger B, Lipset CH. The new normal in clinical trials: decentralized studies. Ann Neurol. 2020;88(5):863–66 (https://doi.org/10.1002/ana.25892).

188. Chatterjee M. Avoiding gridlock: the impact of climate on electric grids [website]. Zurich: Swiss Re Institute; 2024 (https://www.swissre.com/institute/research/topics-and-risk-dialogues/climate-and-natural-catastrophe-risk/impact-of-climate-on-electric-grids.html).

189. Jiménez Cisneros BE, Oki T, Arnell NW, Benito G, Cogley JG, Döll P, Jiang T et al. Freshwater resources. In: Field CB, Barros VR, Dokken DJ, Mach KJ, Mastrandrea MD, Bilir TE et al., editors. Climate Change 2014: impacts, adaptation, and vulnerability. Part A: global and sectoral aspects. Contribution of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge: Cambridge University Press; 2014:229–69 (https://www.ipcc.ch/report/ar5/wg2/).

190. Durairajan R, Barford C, Barford P. Lights out: climate change risk to internet infrastructure. In: ANRW '18: Proceedings of the 2018 Applied Networking Research Workshop, New York, 16 July 2018. New York: Association for Computing Machinery; 2018 (https://doi.org/10.1145/3232755.3232775).

191. Bankhead C. Tropical storm sets back research in Houston. J Natl Cancer Inst. 2001;93(18):1366–7 (https://doi.org/10.1093/jnci/93.18.1366).

192. De Guzman RB, Malik M, Singh N, Ho-Fung Loong H, Mohan A. Lung cancer in Asia: the impact of climate change. EClinicalMedicine. 2024;74:102680 (https://doi.org/10.1016/j.eclinm.2024.102680).

193. Uschner D, Sverdlov O, Carter K, Chipman J, Kuznetsova O, Renteria, J et al. Using randomization tests to address disruptions in clinical trials: a report from the NISS Ingram Olkin Forum series on unplanned clinical trial disruptions. Stat Biopharm Res. 2023;16(4):405–13 (https://doi.org/10.1080/19466315.2023.2257894).

194. Smit B, Pilifosova O, Burton I, Challenger B, Huq S, Klein R et al. Adaptation to climate change in the context of sustainable development and equity. In: McCarthy JJ, Canziani O, Leary NA, Dokken DJ, White KS, editors. Climate Change 2001: impacts, adaptation and vulnerability. Cambridge: Cambridge University Press; 2001:877–912 (https://www.ipcc.ch/report/ar3/wg2/chapter-18-adaptation-to-climate-change-in-the-context-of-sustainable-development-and-equity/).

195. Ziervogel G, Enqvist J, Metelerkamp L, van Breda J. Supporting transformative climate adaptation: community-level capacity building and knowledge co-creation in South Africa. Clim Policy. 2020;22(5):607–22 (https://doi.org/10.1080/14693062.2020.1863180).

196. Quintana AV, Venkatraman R, Coleman SB, Martins D, Mayhew SH. COP26: an opportunity to shape climate-resilient health systems and research. Lancet Planet Health. 2021;5(12):e852–3 (https://doi.org/10.1016/S2542-5196(21)00289-8).

197. Schwerdtle PN, Ngo TA, Hasch F, Phan TV, Quitmann C, Montenegro-Quiñonez CA. Climate change resilient health facilities: a scoping review of case studies in low and middle-income countries. Environ Res Lett. 2024;19(7):074041 (https://doi.org/10.1088/1748-9326/ad472b).

198. Corvalan C, Villalobos Prats E, Sena A, Campbell-Lendrum D, Karliner J, Risso A. Towards climate resilient and environmentally sustainable health care facilities. Int J Environ Res Public Health. 2020;17(23):8849 (https://doi.org/10.3390/ijerph17238849).

199. Harrington J, Felker GM, Mentz RJ. Catastrophic disruptions in clinical trials. Circulation. 2022;146(5):369–71 (https://doi.org/10.1161/CIRCULATIONAHA.122.060541).

200. Hopp WJ, Brown L, Shore C, editors. Causes and consequences of medical product supply chain failures. In: Building resilience into the nation's medical product supply chains. Washington, DC: National Academies Press; 2022: 95–133 (https://www.ncbi.nlm.nih.gov/books/NBK583734/).

201. Ghadge A, Wurtmann H, Seuring S. Managing climate change risks in global supply chains: a review and research agenda. Int J Prod Res. 2018;58(1):44–64 (https://doi.org/10.1080/00207543.2019.1629670).

202. The Great Texas Freeze: February 11–20, 2021 [news release]. National Centers for Environmental Information; 24 February 2023 (https://www.ncei.noaa.gov/news/great-texas-freeze-february-2021).

203. Sheridan K. How blackouts, fires, and a pandemic are driving shortages of pipette tips — and hobbling science [news release]. STAT; 28 April 2021 (https://www.statnews.com/2021/04/28/pipette-tips-shortage/).

204. Nakano K. Risk assessment for adaptation to climate change in the international supply chain. J Clean Prod. 2021;319:128785 (https://doi.org/10.1016/j.jclepro.2021.128785).

205. What science can do: AstraZeneca Task Force on Climate-related Financial Disclosures Statement 2023. Cambridge: AstraZeneca; 2023 (https://www.astrazeneca.com/sustainability/resources.html).

206. Castro-Vincenzi J, Khanna G, Morales N, Pandalai-Nayar N. Weathering the storm: supply chains and climate risk. Cambridge, MA: National Bureau of Economic Research; 2024 (https://www.nber.org/papers/w32218).

207. Completing the picture: how the circular economy tackles climate change. Cowes: Ellen MacArthur Foundation; 2021 (https://www.ellenmacarthurfoundation.org/completing-the-picture).

208. Mehtsun WT, Hyland CJ, Offodile AC 2nd. Adopting a circular economy for surgical care to address supply chain shocks and climate change. JAMA Health Forum. 2023;4(11):e233497 (https://doi.org/10.1001/jamahealthforum.2023.3497).

209. NAP Trends [website]. International Institute for Sustainable Development; 2025 (https://trends.napglobalnetwork.org/).

210. United Nations Office for Disaster Risk Reduction, World Meteorological Organization. Global status of multi-hazard early warning systems 2023. Geneva: United Nations Office for Disaster Risk Reduction; 2023 (https://www.undrr.org/reports/global-status-MHEWS-2023).

Annex 1. Questions guiding discussions with clinical trial actors

The following questions were used to guide conversations with contributors.

1. Could you tell us about your role and experience in clinical trials and describe some projects you have been involved with?
2. What types of trials do you work on?
3. How do you recruit for your trials?
4. When making decisions about trial design (in LMICs), what criteria need to be considered?
5. Have you ever considered the environmental concerns associated with clinical trials? And if so, how could these concerns fit into assessments alongside other criteria?
6. What do you need to know to include environmental concern considerations into your contribution to trials?
7. If there was guidance around how to include environmental concerns in trial design, what barriers could you see emerging when implementing it?
8. Are there any key considerations you would like to see implemented with regards to clinical trials regulation and environmental harm?
9. Who do you think should bear “responsibility” for addressing the environmental impact of trials?
10. Which aspects of clinical trial design (in LMICs) might you consider most vulnerable to climate shocks?
11. Have you ever experienced examples of climate adaptation strategies in the context of clinical trials (in LMICs)?

Annex 2: Review of legislation, regulations and guidelines governing clinical trials

This annex includes a document review of legislation, regulations and guidelines governing clinical trials in WHO Member States. The study team began by reviewing a database of documents pertaining to clinical trial governance collected by WHO.

Relevant documents within the database were searched with keywords to identify content relating to three primary areas: carbon emissions, broader environment considerations and research waste. These keywords were "climate", "carbon", "greenhouse gas", "GHG", "environmental" and "waste". For each of these keywords any mentions were noted, but the documents were only considered if they proved to be of relevance to the overall project. For example, where a document contained the keyword "environment", but it was in the context of a country's overall "research environment", this was marked as "'environment' mentioned but not relevant to report".

Table A2.1 shows the countries on which relevant information was found, and reports the context in which keywords appear. It contains the full document review, including countries for which no relevant documentation was available or keyword searches returned no findings.

The team also identified countries for which:

- no documents were available to review within the database
- documents were available to review but could only be found in a foreign language.

These countries were ruled out of the document review and are marked "N/A" in Table A2.2.

Findings

Of 194 WHO Member States, documents from 67 countries were included in the search (document links were supplied by WHO). Of those, 59 had clinical trial governance documents that were reviewable in English, including documents automatically translated by Google. Following keyword searches, 20 documents contained text relevant to the project. Specifically, no documents contained the keywords "carbon" or "GHGs"; the keyword "climate" was present in two documents from two countries (Singapore and Viet Nam); 3 documents from Argentina, Canada and Malaysia contained the keyword "waste" (in the context of research waste); and 17 documents (from 16 countries) contained the keyword "environment" in a relevant context. Table A1 summarizes the findings.

The analysis identified a number of key points of interest:

- Reading around the keywords, only two documents alluded to any aspect of intergenerational justice. In Singapore's Ethics guidelines for human biomedical research, the term "climate" was used in the context of "sustainability", and the principle that research should not prejudice the welfare of future generations was mentioned. Cameroon's Law No. 2022/008, Relating to Medical Research Involving Human Subjects in Cameroon discusses "environment" in the context of the "protection of future generations, the environment, the biosphere, biodiversity" acting as a guiding principle of medical research.
- The Democratic Republic of the Congo's Guidelines for the ethical review of research in the

Democratic Republic of Congo uses "environment" in the context of "collective consent", which is required when conducting research involving "traditional knowledge or the sacred rights of an indigenous community". The guidelines state that information must be provided to participants on a "preliminary assessment of likely environmental factors" in order for this collective consent to be "informed". The clause is interesting because it implies that populations participating in clinical trials in the Democratic Republic of the Congo should be aware of a trial's environmental impact in order to be capable of providing informed consent.

- "Waste" was surprisingly not a common keyword, given the well-established problem of research waste within clinical research.
- "Environment" was often used in general discussions about medical waste or genetically modified organisms. In combination with the missing discussion on "climate", this suggests that other environmental impacts associated with clinical trials – such as climate change – are being severely underestimated in national governance.
- "Best-performing" countries Malaysia and Viet Nam were the only two to have governance documents with more than two relevant appearances of different keywords. Malaysia was also the only country to have two separate documents with keyword appearances. Indeed, the Malaysian code of responsible conduct in research also raised some forward-thinking possibilities as it discussed funders' responsibilities towards the environment. Specifically, when the document discusses "funders' responsibility to ensure that projects make the biggest possible contribution", it includes "the environment" in the list of factors to be considered. This was also the only document that considered the responsibilities of ethics review boards towards the environment. In particular, it stated that "research misconduct" can take place when research does not take place "as approved by ethical review boards" and has "detrimental effects" on the environment.

Table A2.1. Review of documents from WHO Member States for which relevant information appeared in the keyword search

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
Argentina	Ministry of Health National Administration of Food, Drugs and Technology	Ministerial Resolution 1480/2011 Approving the Guidelines for Human Health Research and Creating the National Registry of Health Research	None	None	None	"Environment" mentioned but not relevant to report	"Waste" mentioned twice: once in relation to "scientific validity", stating invalid studies waste resources; once in relation to the "social value of research", saying that research of little social value "wastes resources"
Bangladesh	Ministry of Health and Family Welfare Directorate-General of Drug Administration Bangladesh Medical Research Council	Drugs and Cosmetics Act, 2023	None	None	None	None	None
		The Bengal Drug Rules, 1946	None	"Carbon" mentioned but not relevant to report	None	None	None
		Ethical guidelines for conducting research studies involving human subjects, 2013	None	None	None	"Environment" mentioned once relevant to report in discussion of requirement for an environmental impact assessment for Phase III clinical trials	"Waste" mentioned but not relevant to report
Bosnia and Herzegovina	Ministry of Health of Federation of Bosnia and Herzegovina	Medical Products and Device Act 2008	None	None	None	"Environment" mentioned five times: once not relevant to report; once in relation to the "risks associated with medicinal product use"; twice related to the "application for issuing a marketing of medicinal products authorization"; and once in relation to the "disposal of pharmaceutical waste"	"Waste" mentioned but not relevant to report
Brazil	National Health Surveillance Agency	Resolution No. 945, 2024	None	None	None	"Environment" mentioned twice: once not relevant to report; once in relation to genetically modified organism products	None
		Regulatory Instruction – In No. 338, 2024	None	None	None	None	None
Cameroon	Ministry of Public Health Cameroon	Law No. 2022/008, Relating to Medical Research Involving Human Subjects in Cameroon	None	None	None	"Environment" mentioned once, listing the "protection of future generations, the environment, the biosphere, biodiversity" as a guiding principle of medical research	None
Canada	Health Canada	Part C, Division 5 of the Food and Drug Regulations – "Drugs for Clinical Trials Involving Human Subjects", 2023	None	None	None	"Environment" mentioned but not relevant to report	None
		Tri-Council Policy Statement 2, 2022	None	None	None	None	"Waste" mentioned twice: once not relevant to report; once in relation to a failure to disseminate research results, stating it "wastes resources"
Croatia	Ministry of Health	Medicinal Products Act, 2013	None	None	None	"Environment" mentioned four times: all in relation to the risks the medicinal product could pose to the environment	"Waste" mentioned but not relevant to report
		Ordinance on Clinical Drug Trials and Good Clinical Practice, 2015	None	None	None	None	None
Cuba	Ministry of Public Health Center for State Control of Medicines and Medical Devices	N/A	N/A	N/A	N/A	N/A	N/A

Table A2.1. Review of documents from WHO Member States for which relevant information appeared in the keyword search *(continued)*

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
Democratic Republic of the Congo	Congolese Pharmaceutical Regulatory authority	*Guidance on pharmacovigilance in the Democratic Republic of the Congo*, 2018	None	None	None	"Environment" mentioned but not relevant to report	None
		Guidelines for the ethical review of research in the Democratic Republic of the Congo, 2011	None	None	None	"Environment" mentioned once in relation to the "collective consent" required when conducting research involving "traditional knowledge or the sacred rights of an indigenous community", stating that information must be provided to participants on a "preliminary assessment of likely environmental factors" in order for this collective consent to be "informed"	None
Egypt	Egyptian Drug Authority	*Guideline for good regulatory oversight of clinical trials by the Egyptian Drug Authority*, 2024 (Note: guidelines only)	None	None	None	"Environment" mentioned twice: both in relation to accreditation required for destruction of medicinal products and human surplus	None
Liberia	Liberia Medicines and Health Products Regulatory Authority	Regulations on Clinical Trials, 2022	None	None	None	"Environment" mentioned once in relation genetically modified organisms	None
Malawi	Pharmacy and Medicines Regulatory Authority	Pharmacy and Medicines Regulatory Authority Act, 2019	None	None	None	"Environment" mentioned three times: once in relation to the disposal of medicines; twice in relation to prohibition notices that may be issued if there is a "risk to the environment"	None
		National Policy Measures for the Improvement of Health Research Coordination in Malawi, 2003	None	None	None	None	None
Malaysia	Ministry of Health Malaysia	Act 368, Sales of Drugs Act, 1952 (revised 1989)	None	None	None	None	None
	National Science Council	Control of Drugs and Cosmetics Regulations, 1984	None	None	None	None	None
	Malaysian Medical Council	*Malaysian code of responsible conduct in research*, 2020	None	None	None	"Environment" mentioned 14 times, five of which are relevant to the report: two in relation to a "duty of care" and "respect" for the environment on the part of researchers; one describing funders' responsibilities to ensure that research contributes to "the environment"; one describing the ethical requirements to avoid "detrimental effects" towards the environment; one describing conduct that can lead to "adverse effects on the environment" as breach of the code worthy of investigation	"Waste" mentioned twice: once in relation to the careful use of resources, stating that "waste and duplication" should be avoided; once stating that "duplication, unless for verification, is wasteful of resources and is deemed unethical and should be avoided"
		Guideline of Malaysian Medical Council, Clinical Trials and Biomedical Research, 2006	None	None	None	"Environment" mentioned once, stating that "special caution must be exercised in the conduct of research which may affect the environment"	None
Mexico	Federal Commission for the Protection of Sanitary Rights	Regulation to the General Health Law Regarding Research to Health, 2014	None	None	None	"Environment" mentioned seven times: four not relevant to report; twice regarding the effect of infectious material on the environment; once relating to genetically modified organisms	"Waste" mentioned but not relevant to report
New Zealand	New Zealand Medicines and Medical Devices Research Authority	Guideline on the regulation of therapeutic products in New Zealand, 2024	None	None	None	"Environment" mentioned twice: both in reference to the requirement to contact the New Zealand Environmental Protection Authority regarding the use of new or genetically modified organisms as an investigational product	None

Table A2.1. Review of documents from WHO Member States for which relevant information appeared in the keyword search

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
Nigeria	Federal Ministry of Health	National Code of Health Research Ethics, 2007	None	None	None	"Environment" mentioned three times: twice not relevant to report; once describing the requirement of an institutional biosafety committee to establish that research "on or with classified hazardous substances" does not harm the environment	None
	National Agency for Food and Drug Administration and Control	*Good clinical practise guidelines*, 2020	None	None	None	None	None
Singapore	Ministry of Health	Human Biomedical Research Act 2015	None	None	None	None	None
	Bioethics Advisory Committee Singapore	*Ethics guidelines for human biomedical research*, 2021	"Climate" mentioned once in the context of "sustainability" and the principle that research should not prejudice the welfare of future generations	None	None	"Environment" mentioned but not relevant to report	
Switzerland	Swissmedic	The Clinical Trials Ordinance (ClinO, SR 810.305), 2014	None	None	None	"Environment" mentioned five times: all in relation to clinical trials of gene therapies or genetically modified organisms	None
Uganda	National Drug Authority	The National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014 (S.I. 2014/32)	None	None	None	None	None
	Ugandan National Council for Science and Technology	Guidelines for the conduct of clinical trials in Uganda, 2024	None	None	None	None	"Waste" mentioned but not relevant to report
		Guidelines on good clinical practice in the conduct of clinical trials involving human participants, 2024		None	None	"Environment" mentioned twice: once not relevant to report; once stating "medical research should be conducted in a manner that minimizes possible harm to the environment"	None
Viet Nam	Ministry of Health	Law No. 105/2016/QH13 on Pharmacy	"Climate" mentioned once, specifying that the extraction of natural resources that contribute to Viet Nam's "master plan for pharmacy industry development" must be done in a way that is "appropriate for the climate".	None	None	"Environment" mentioned three times: twice relevant to the cooperation of the Ministry of Natural Resources and Environment with the Ministry of Health in regard to the legislation; once in relation to Viet Nam's "master plan for pharmacy industry development", stating that it must "ensure environmental protection"	None
		Circular No. 29/2018/TT-BYT – Regulation on Clinical Drug Trials	None	None	None	None	"Waste" mentioned but not relevant to report

Table A2.2. Review of clinical trials governance documents from WHO Member States for which relevant information did not appear in the keyword search

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
Afghanistan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Albania	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Algeria	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Andorra	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Angola	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Antigua and Barbuda	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Armenia	Drug and Medical Technology Agency Ethics Committee of the Ministry of Health	Resolution of the Government of Armenia of 24 January 2002: Procedure for Clinical Trials of New Medications in Armenia	None	None	None	None	None
Australia	Therapeutic Goods Association National Health and Medical Research Council	Therapeutic Goods Act 1989 Therapeutic Goods Regulations 1990 Therapeutic Goods (Medical Devices) Regulations 2002 *National Statement on Ethical Conduct in Human Research 2023*	None None None	None None None	None None None	"Environment" mentioned but not relevant to report "Environment" mentioned but not relevant to report "Environment" mentioned but not relevant to report None	"Waste" mentioned but not relevant to report "Waste" mentioned but not relevant to report "Waste" mentioned but not relevant to report
Austria	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Azerbaijan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bahamas	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bahrain	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Barbados	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Belarus	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Belgium	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Belize	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Benin	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bhutan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bolivia (Plurinational State of)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Botswana	Ministry of Health and Wellness, Botswana	Drugs and Related Substances, Act No. 18, 1992 *Guidelines for regulating the conduct of clinical trials using medicines in human participants*, 2012	Carbon mentioned but not relevant to report None	None None	None None	None None	None None
Brunei Darussalam	Ministry of Health Brunei Darussalam	Brunei Darussalam guidelines for good clinical practice, 2008 (*Note:* guidelines only)	None	None	None	None	None
Bulgaria	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Burkina Faso	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table A2.2. Review of clinical trials governance documents from WHO Member States for which relevant information did not appear in the keyword search *(continued)*

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
Burundi	East African Community (*Note:* a non-national, regional body)	*Compendium of medicines evaluation and registration for medicine regulation harmonization in the East African Community*, 2019	None	None	None	"Environment" mentioned but not relevant to report	None
Cabo Verde	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cambodia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Central African Republic	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chad	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chile	Ministry of Health of Chile Public Health Institute of Chile	Law 20.120, 2006 – On Scientific Research Into Human Beings, Their Genomes, and Prohibition of Human Cloning	None	None	None	None	None
China (*Note:* most legislation and regulations not available in English)	National Medical Products Association National Health Commission	NMPA-GCP-No57-2020	None	None	None	None	None
Colombia	The National Institute of Drug and Food Surveillance	N/A	N/A	N/A	N/A	N/A	N/A
Comoros	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Congo	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cook Islands	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Costa Rica	Ministry of Health National Health Research Council	Biomedical Research Regulatory Law – No. 9234, 2014 Reform of the Regulations to Biomedical Research Regulatory Law, NO. 39533-S, 2015	None None	None None	None None	None None	None None
Côte d'Ivoire	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cyprus	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Czechia	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Democratic People's Republic of Korea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Denmark	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Djibouti	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Dominica	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Dominican Republic	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ecuador	N/A	N/A	N/A	N/A	N/A	N/A	N/A
El Salvador	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Equatorial Guinea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Eritrea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Estonia	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Eswatini	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethiopia	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table A2.2. Review of clinical trials governance documents from WHO Member States for which relevant information did not appear in the keyword search *(continued)*

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
EU	European Commission European Medicines Agency	Regulation (EU) No 536/2014 Directive 2005/28/EC	None None	None None	None None	"Environment" mentioned but not relevant to report None	None None
Fiji	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Finland	See EU	See EU	See EU	See EU	See EU	See EU	See EU
France	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Gabon	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gambia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Georgia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Germany	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Ghana	Food and Drugs Authority	Public Health Act, Act 851, 2012	None	None	None	"Environment" mentioned but not relevant to report	None
Greece	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Grenada	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Guatemala	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Guinea	Ministry of Health and Public Hygiene	L/2018/024/AN – Law Relating to Medicines, Health Products, and the Exercise of the Profession of Pharmacists	None	None	None	None	None
Guinea-Bissau	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Guyana	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Haiti	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Honduras	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hungary	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Iceland	Ministry of Welfare	Regulation on clinical trials of medicinal products in humans, No. 443/2004, as amended by Regulations No. 907/2004 and No. 1099/2010	None	None	None	None	None
India	The Central Drugs Standard Control Organization The Drug Controller General of India Indian Council of Medical Research	New Drugs and Clinical Trials Rules, 2019. *Handbook for applicants and reviewers of clinical trials of new drugs in India*	None None	None None	None None	"Environment" mentioned but not relevant to report "Environment" mentioned but not relevant to report	"Waste" mentioned but not relevant to report None
Indonesia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Iran (Islamic Republic of)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Iraq	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ireland	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Israel	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Italy	See EU	See EU	See EU	See EU	See EU	See EU	See EU

Table A2.2. Review of clinical trials governance documents from WHO Member States for which relevant information did not appear in the keyword search *(continued)*

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
Jamaica	Ministry of Health Ethics and Medico-Legal Affairs Panel	Food and Drugs Act, 1975 *Ministry of Health guidelines for the conduct of research on human subjects*	None None	None None	None None	None None	None None
Japan	Ministry of Health, Labour and Welfare Pharmaceuticals and Medical Devices Agency	Clinical Trials Act Pharmaceutical and Medical Device Act	None None	None None	None None	None None	None None
Jordan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kazakhstan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kenya	Pharmacy and Poisons Board National Commission for Science, Technology and Innovation	Pharmacy and Poisons Act, Chapter 224, 2023 Pharmacy and Poisons (Conduct of Clinical Trials) Rules, 2022	None None	None None	None None	None "Environment" mentioned but not relevant to report	None "Waste" mentioned but not relevant to report
Kiribati	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kuwait	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kyrgyzstan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lao People's Democratic Republic	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Latvia	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Lebanon	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lesotho	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Libya	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lithuania	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Luxembourg	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Madagascar	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Maldives	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mali	Directorate of Pharmacy and Medicine	Decree No. 2017-0245 – Establishing the Terms of Application of Law No. 09-059 Governing Biomedical Research on Humans	None	None	None	"Environment" mentioned but not relevant to report	None
Malta	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Marshall Islands	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mauritania	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mauritius	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Micronesia (Federated States of)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Monaco	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mongolia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Montenegro	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morocco	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mozambique	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Myanmar	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table A2.2. Review of clinical trials governance documents from WHO Member States for which relevant information did not appear in the keyword search *(continued)*

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
Namibia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nauru	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nepal	Nepal Health Research Council	Nepal Health Research Council Act, 2047 – 1991	None	None	None	None	None
Netherlands (Kingdom of the)	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Nicaragua	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Niger	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Niue	N/A	N/A	N/A	N/A	N/A	N/A	N/A
North Macedonia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Norway	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Oman	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pakistan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Palau	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Panama	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Papua New Guinea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Paraguay	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Peru	National Institute of Health	N/A	N/A	N/A	N/A	N/A	N/A
Philippines	Department of Health Department of Science and Technology	*Regulation of clinical trials in the Philippines*, 2012	None	None	None	None	None
Poland	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Portugal	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Qatar	Qatar Supreme Council of Health	*Policies, regulations and guidelines for research involving human subjects*	None	None	None	"Environment" mentioned but not relevant to report	None
Republic of Korea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Republic of Moldova	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Romania	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Russian Federation	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rwanda	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Saint Kitts and Nevis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Saint Lucia	Ministry of Health, Wellness and Elderly Affairs	Clinical Trials Act, 2016	None	None	None	None	None
Saint Vincent and the Grenadines	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Samoa	N/A	N/A	N/A	N/A	N/A	N/A	N/A
San Marino	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sao Tome and Principe	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Saudi Arabia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Senegal	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table A2.2. Review of clinical trials governance documents from WHO Member States for which relevant information did not appear in the keyword search *(continued)*

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
Serbia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Seychelles	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sierra Leone	Ministry of Health and Sanitation Pharmacy Board of Sierra Leone	The Pharmacy and Drugs Act, 2001 *Guidelines for application and authorization of clinical trials of medicines, vaccines, medical devices and food supplements in Sierra Leone*	None None	None None	None None	None None	None None
Slovakia	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Slovenia	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Solomon Islands	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Somalia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
South Africa	South African Health Products Regulatory Authority	Medicines and Related Substances Act, No. 101 of 1965 National Health Act, 2003 (Act No. 61 of 2003) – Regulations Relating to Research with Human Participants	None None	None None	None None	None None	None None
South Sudan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Spain	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Sri Lanka	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sudan	National Ministry of Health	*National guidelines for ethical conduct of research involving human subjects*, 2008	None	None	None	"Environment" mentioned but not relevant to report	None
Suriname	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sweden	See EU	See EU	See EU	See EU	See EU	See EU	See EU
Syrian Arab Republic	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tajikistan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Thailand	Thai Food and Drug Administration Forum of Ethical Review Committees in Thailand	Drug ACT B.E.2510 (A.C. 1967) Ethical guidelines for research on human subjects in Thailand, 2007	None None	None None	None None	None "Environment" mentioned but not relevant to report	None None
Timor-Leste	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Togo	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tonga	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Trinidad and Tobago	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tunisia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Türkiye	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Turkmenistan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tuvalu	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ukraine	Ministry of Health	*Procedure for conducting clinical trials of medicinal products and expert evaluation of materials pertinent to clinical trials*, 2009	None	None	None	None	None

Table A2.2. Review of clinical trials governance documents from WHO Member States for which relevant information did not appear in the keyword search *(continued)*

Country reviewed	Relevant agencies	Relevant documents	Mention of "climate"	Mention of "carbon"	Mention of "GHGs"	Mention of "environment"	Mention of "waste"
United Arab Emirates	N/A	N/A	N/A	N/A	N/A	N/A	N/A
United Kingdom of Great Britain and Northern Ireland	Medicines and Healthcare products Regulatory Agency	The Medicines for Human Use (Clinical Trials Regulations 2004	None	None	None	None	None
		The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006	None	None	None	None	None
United Republic of Tanzania	Tanzania Medicines and Medical Devices Authority	Tanzania Medicines and Medical Devices Act, 2019	None	None	None	"Environment" mentioned but not relevant to report	None
	Tanzania Commission for Science and Technology	Tanzania Food, Drugs, and Cosmetics Act (Clinical Trials Control), 2013	None	None	None	None	None
United States of America	Food and Drug Administration	21 CFR Part 312 – Investigational New Drug Application	None	None	None	"Environment" mentioned but not relevant to report	"Waste" mentioned but not relevant to report
		21 CFR Part 56 – Institutional Review Boards	None	None	None	"Environment" mentioned but not relevant to report	None
Uruguay	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Uzbekistan	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vanuatu	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Venezuela (Bolivarian Republic of)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yemen	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Zambia	Ministry of Health National Health Research Authority	National Health Research Act, 2013	None	None	None	None	None
Zimbabwe	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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