Understanding current thinking around carbon emission impact assessment and clinical trials regulation

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Report produced as part of the work of the MRC-NIHR Trials Methodology Research Partnership Greener Trials Group

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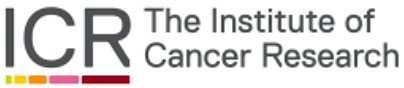

Executive summary

Clinical trials are critical to the evaluation of the safety, efficacy and effectiveness of clinical interventions. However, each trial is responsible for the generation of substantial quantities of greenhouse gasses, contributing to climate change, which itself has major implications for human health. With approximately 38,000 new trials registered globally on Clinicaltrials.gov in 2022[1], achieving national and international healthcare emissions targets will require concerted efforts to reduce emissions associated with clinical trials.

There is growing interest in reducing the carbon[2] emissions associated with both publicly-funded and industry-led clinical trials ('mitigation'). Increasingly, evidence is being generated on the carbon emissions of individual trials, and tools for assessing these emissions are becoming available. Funders and other bodies have published a range of guidance materials to support efforts within the clinical trial community to reduce carbon impacts.

This report represents the output of an Innovate UK grant awarded to members of the MRC-NIHR Trials Methodology Research Partnership Greener Trials Working Group. Major activities included (a) a half-day cross-sectoral knowledge exchange and discussion event to discuss potential regulatory solutions to clinical trial carbon emission mitigation, (b) a short landscaping of the authors' networks to determine potential regulatory barriers impeding such mitigation, and (c) a regulatory document review of current major international authority regulations governing clinical trials for content pertaining to mitigation carbon emissions.

Participants in the half-day cross-sectoral knowledge exchange concluded that, after a slow start, **substantial progress is now beginning to be made** in the consideration of clinical trials' associated carbon emissions.

Participants argued that **this momentum needed to be maintained**, with all interest holders within the clinical trial ecosystem – including academic and industry researchers, funders, regulators and ethics committees, academic publishers, higher education institutions, healthcare organisations, professional societies, trade associations, and patients and carers – having a part to play in advancing the agenda.

A key challenge was identifying how to capitalise on the widespread consensus on the need for action to accelerate progress. Participants argued that **greater coordination was needed *within* various key interest holder groups**, including funders and regulators, to facilitate speedy adoption of greener practices by the clinical trials community. Harmonised approaches would ensure that there are consistent requirements on trialists which would minimise unnecessary additional work to satisfy the individual needs of different organisations.

Given that there are also significant interdependencies within the clinical trials ecosystem, **coordination *across* different interest holder groups** was also felt to be important. This will ensure that objectives and recommended practices are compatible and aligned, for example across funders, publishers and regulatory authorities. A **forum or convening body**, acting as an 'honest broker' could play a critical role in bringing different interest holders together to ensure a cohesive approach is developed across the

[1] https://clinicaltrials.gov/about-site/trends-charts

[2] When we use the term 'carbon', we are referring to all greenhouse gas emissions.

entire clinical trials ecosystem. Ideally, alignment would extend internationally, given that many trials take place in multiple countries.

Nevertheless, many knowledge gaps exist, and **continuing work is needed to build the evidence base** on the most effective ways to reduce emissions, including academic research and case studies. This new knowledge and experience can inform the development of expected best practice and guidance for the clinical trials community. However, given the incompleteness of data and speed at which progress is required to address the climate crisis, it was felt that some **flexibility should be retained** to allow for rapid updating, so as not to stifle innovation.

In summary, at this inflexion point, the tools are increasingly becoming available to measure and reduce the carbon emissions of clinical trials. A key challenge now is not just to refine methodologies and collect more data, but to identify **how different interest holders within the clinical trials ecosystem can work cooperatively, and ensure regulation works to enable greener practices, to optimise their use and potential to reduce emissions**.

In particular, **regulatory authorities** have a potentially critical influence on what research is carried out and how it is carried out. Further cross-sectoral dialogue is therefore needed to ensure that regulatory policies enable a shift towards greater sustainability in the clinical trials ecosystem. This was further highlighted by the results of our document review and landscaping exercise, both of which highlighted the ways in which **regulation is lagging behind and producing a range of regulatory barriers impeding clinical trials carbon mitigation.** To address this shortfall, carbon emissions associated with trials need to be considered by multiple groups, including sponsors, funders, ethics committees, regulators and publishers. The key challenge is to determine how further progress can be made, without compromising or slowing the development of much-needed medical innovations.

Contents

1. Introduction

Clinical trials are critical to the evaluation of new health interventions and, as argued by the recent O'Shaughnessy Review into commercial clinical trials in the UK[3], they should be considered a fundamental part of health and social care.

Essential though they are, clinical trials inevitably contribute to global greenhouse emissions. An estimated 38,000 new trials were registered on clinicaltrials.gov in 2022, each with an estimated carbon footprint of 80–2000 tonnes of carbon dioxide equivalent (CO_2e). Even at the lower end of estimates, these numbers are significant – 80 tonnes is equivalent to driving a car ten times around the planet.

Carbon emissions are associated with multiple aspects of clinical trials. These include emissions associated with the **manufacturing** and distribution of the medicinal products, medical devices and other interventions being evaluated, or with implementation of educational or programmatic interventions. In addition, there are emissions associated with a trial's **research processes**, such as the patient assessments, energy consumption of facilities, research associated travel of investigators and participants, and emissions linked to laboratory investigations during and after trials.

Climate change and the drive towards net zero is an overarching challenge that affects all interest holders within the clinical trials ecosystem. As well as those planning and conducting research, other groups have significant leverage on how research activities are carried out. These include the **sponsors** who design, conduct and report the trial, the **funders** who review proposals and decide whether to support studies, **academic publishers**, who are the gatekeepers controlling access to the results of research and can apply conditions on publication, and **regulators**, who must approve clinical study applications (and ultimately license new interventions). The potential importance of both research ethics committees[4] and national/international regulatory authorities[5] has been noted.

Key issues include how a low carbon agenda can be advanced without compromising the ability of clinical trials to deliver patient benefits, patient safety, or inhibiting the adoption of innovative practices. In addition, there is a need to consider who should have responsibility for promoting more carbon-aware practice or enforcing such requirements.

However, while as discussed at a recent meeting of the Academy of Medical Sciences[6], there is growing interest in minimising the carbon footprint of medical research, many of these initiatives have focused on laboratory research and, until recently, comparatively less attention has been given to clinical trials[7]. This is despite some pioneering work on carbon auditing of trials carried out more than a decade ago[8]. Nevertheless, some groups have begun to examine the sustainability of clinical trials, including the

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[3] https://www.gov.uk/government/publications/commercial-clinical-trials-in-the-uk-the-lord-oshaughnessy-review

[4] McMichael AJ, Bambrick HJ. Greenhouse-gas costs of clinical trials. Lancet. 2007;369(9573):1584-5. doi: 10.1016/S0140-6736(07)60725-9.

[5] Rahman S, Ryan S, Kim J, Kenney P, Ghali F. Clinical Trials and Climate Change: Doing Our Part While Pursuing Progress. Eur Urol Focus. 2023;9(6):861-862. doi: 10.1016/j.euf.2023.11.011.

[6] https://acmedsci.ac.uk/file-download/61695123

[7] Adshead F, Al-Shahi Salman R, Aumonier S et al. A strategy to reduce the carbon footprint of clinical trials. Lancet. 2021;398(10297):281-282. doi: 10.1016/S0140-6736(21)01384-2.

[8] 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. doi: 10.1186/1745-6215-12-31.

MRC-NIHR Trials Methodology Research Partnership Greener Trials Working Group[9]. The Sustainable Healthcare Coalition also provides a forum for dialogue across the academic and industry healthcare sector, while the Research and Development Forum has created a Sustainability Working Group across the health and care community.

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[9] http://www.methodologyhubs.mrc.ac.uk/about/working-groups/trial-conductwg/tcwg-subgroup-greener-trials/

2. Workshop

On 28th June 2024, 32 representatives across the UK clinical trials sector were convened for a half day workshop at the Wellcome Collection, UK. The aim of the workshop was to take stock of the current situation and how efforts to reduce clinical trial carbon emissions can be advanced. The meeting included representatives from academia, the health service, journals, industry, funding bodies, regulatory authorities and patients and the public. Representatives were selected via the authors' existing network of clinical-trial interest holders and via snowballing. The workshop agenda is listed in Appendix A.1 and the workshop attendees are listed in Appendix A.2.

2.1 Workshop format

The morning began with three presentations from speakers representing academia, industry and funding bodies, as well as reflections from patient representatives. The group then split into five breakout sessions to discuss the question that had been sent to attendees prior to the workshop:

> **Should regulatory, ethics review, funding or other relevant bodies consider assessments of the environmental impact of clinical trials?** Consider each group in turn, as well as how (if at all) this would work in practice, and potential barriers and/or opportunities for innovation.'

Breakout groups returned to the plenary to share highlights from their discussions, and reflect on the themes and challenges arising during the morning's discussion.

Note: the workshop focused on the design of clinical trials, including carbon emissions associated with the interventions being evaluated. It did not cover other environmental impacts of clinical trials, such as water use and waste production.

2.2 Workshop presentations

Representatives from critical sectors gave short presentations on key issues and the current situation. This included presentations by Dr. Lisa Fox of the Institute of Cancer Research, Dr. Neil MacKillop of AstraZeneca, and Jennifer Ekelund of National Institute of Health and Care Research, as well as reflections from patient representatives Amanda Roberts and Ray Gardner.

2.2.1 Academia

After a relatively slow start, more experience has been gained in **quantifying the carbon footprint** of publicly funded clinical trials. More trials have been analysed and tools developed for footprinting all stages of trials[10]. Multiple different aspects of trial design can be quantified, such as patient assessments, emissions from clinical trial unit (CTU) facilities, meetings and travel, laboratory activities, and data collection and exchange.

[10] 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. doi: 10.1136/bmjopen-2023-075755.

A recent analysis of data from 12 academic trials indicates that footprinting a trial takes 5–60 hours, dependent largely on people's familiarity with tools and clinical trial[11]. Carbon footprinting does not require high levels of technical knowledge and can be conducted by people with a range of roles in trials. The analysis also suggests that it is not possible to make broad-brush assumptions about the emissions associated with particular trial activities, so trials need to be analysed individually. More data are needed, as well as continued analysis of emerging hotspots.

2.2.2 Industry

Some pharmaceutical companies, including AstraZeneca[12], have made a strategic commitment to sustainability, which in some cases are written into formal company strategy. These commitments can cover direct company emissions and those of their supply chain. Companies can adopt generic sustainability policies, such as use of electric vehicles and making a commitment to use renewable energy, as well as minimising the carbon impact of trials and product manufacturing.

Companies such as AstraZeneca have developed in-house tools for quantifying the carbon footprint of trials, and using these analyses to inform trial design. The most impactful activities on a carbon bottom line include trial-associated travel and the tissue sample life cycle (from sample collection through analysis)[13].

Through collaboration via the Sustainable Markets Initiative[14] and as part of its commitment to decarbonising AstraZeneca plans to report the footprint of its late stage clinical trials from 2025.

2.2.3 Funders

Multiple initiatives have addressed monitoring and reduction of the carbon footprint of laboratory research. The NIHR has developed **carbon reduction guidelines for health research[15]**, which cover clinical trials and are currently being updated.

Some funders, including the NIHR, fund studies to generate evidence on the best approaches for carbon reduction. The NIHR is launching a specific call in November 2024 on decarbonising health and social care systems. Researchers can also apply for funding to supplement existing grants in order to carry out related carbon monitoring and reduction studies.

2.2.4 Patients

As the ultimate beneficiaries of the interventions being evaluated, patients have a key interest in clinical trials. A key principle is that efforts to reduce carbon emissions in clinical trials should not be at the expense of patient safety or unnecessarily hamper the ability of trialists to conduct research, which could slow the development of medical innovations.

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[11] Griffiths J, Adshead F, Al-Shahi Salman R et al. Quantifying the carbon footprint of academic clinical trials: building the evidence base and hotspot identification. Research Square. https://doi.org/10.21203/rs.3.rs-4363597/v1

[12] https://www.astrazeneca.com/sustainability.html

[13] Mackillop N, Shah J, Collins M, Costelloe T, Öhman D. Carbon footprint of industry-sponsored late-stage clinical trials. BMJ Open. 2023 Aug 21;13(8):e072491. doi: 10.1136/bmjopen-2023-072491.

[14] The Sustainable Markets Initiative is a global private sector organisation with the mission to "to build a coordinated global effort to enable the private sector to accelerate the achievement of global climate, biodiversity and Sustainable Development Goal targets." https://www.sustainable-markets.org/

[15] https://www.nihr.ac.uk/documents/nihr-carbon-reduction-guidelines/21685

2.2.5 Regulators

Due to the 2024 General Election that was called before the workshop took place, the UK's two main regulatory agencies, the Health Research Authority (HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA), were not able to actively participate in the workshop. However, the HRA subsequently provided comments on the workshop proceedings which have been incorporated into this section.

Whilst the HRA has not developed or designed specific guidelines with mitigating carbon emissions in mind, there are certain guidelines that both promote certain research standards and could ensure that research has a lower carbon impact. Examples of this guidance include:

- registering research on a public database[16] and publishing the results[17] to avoid the research being repeated
- involving patients and the public[18] in developing research proposals to help design a research project with just the right amount of research activity in just the right places and ways so that the results are more meaningful to the people the research is for and about
- setting up research so that participants can attend appointments locally[19] instead of travelling further afield
- how to seek consent electronically[20] as an alternative option to seeking consent in person, potentially reducing participant and researcher travel.

Additionally, **research ethics committees (RECs)** have a clear remit to consider the risk/benefit ratio and care and protection of participants. Again, whilst they may not currently review studies with the carbon footprint in mind, by reviewing within the guidance and expectations set by the HRA they have the potential to influence a trial's carbon impact by ensuring, for example, that there has been involvement from patients and the public, or that participants can attend appointments locally.

2.3 Key Themes

Discussions at the workshop, identified during breakout groups and brought together in a plenary session, identified a range of key themes:

2.3.1 This is a rapidly evolving area–much progress is being made in academia and industry, and there is a need to maintain the momentum.

There has been a perception that sustainability has not received as much attention within the clinical trial community as in laboratory science[21]. That no longer seems to be the case. Crucially, the **evidence base is growing** and an increasing number of tools are becoming available to quantify the carbon footprint of

[16] https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/
[17] https://www.hra.nhs.uk/planning-and-improving-research/research-planning/publishing-your-research-findings/
[18] https://www.hra.nhs.uk/planning-and-improving-research/best-practice/public-involvement/
[19] https://www.myresearchproject.org.uk/help/hlpinterventional.aspx
[20] https://www.hra.nhs.uk/planning-and-improving-research/best-practice/informing-participants-and-seeking-consent/
[21] https://acmedsci.ac.uk/file-download/61695123

trials. Previously, a widespread desire to adopt greener practices has been held back by uncertainty about the best approaches to take. New tools are helping to overcome this critical barrier, but more publicly-funded and industry specific trial data is required before a common tool can be considered.

The lead has been taken by pioneering organizations and collectives. There is now a need to embed **mainstream green thinking** within routine clinical trial design and management within each sector.

2.3.2 Knowledge exchange and coordination is needed *within* and *across* interest holder groups to ensure consistency in practice and promote alignment around a common agenda.

There is a strong desire within the clinical trials community to adopt greener practices. The adoption of new knowledge and tools to achieve this will be facilitated and accelerated if the key groups that influence clinical trial design adopt **common principles and practices**. This could build on community efforts such as the recently announced Concordat for the Environmental Sustainability of Research and Innovation Practice[22] for the public sector, and the industry-led Sustainable Markets Initiative Health Systems Task Force, which includes a focus on clinical trials.[23] Trials are often global in nature, so a collaborative international approach would also be beneficial. WHO is an additional key global interest holder that needs to be engaged.

All sectors need to play a role in enhancing the sustainability of clinical trials, but there are many **interconnections** – what one interest holder group does impacts on others. For example, regulatory requirements will impact on industry and public research activities, which will affect funding requests; conversely, funders and sponsors need to avoid policies or restrictions that are incompatible with regulatory requirements. Future alignment in the use and application of methodology across sectors would minimise unnecessary duplication of efforts in trial design and reporting, and support the building of expertise in key methodologies. As such, **coordination across sectors** is essential to ensure consistency and alignment and to minimise unnecessary demands on triallists.

In particular, it was felt that **regulators** are likely to be a potentially powerful influence. Depending on the positions adopted, regulators could be critical enablers of greener practice. Conversely, regulatory policies could create barriers to the adoption of greener research practices. Cross-sectoral dialogue will be essential to ensure that regulatory policies are consistent with – and ideally promote – a shift towards greater sustainability in the clinical trials ecosystem.
Furthermore, a **neutral convening body** could potentially play a coordinating and strategic leadership role as an ‘honest broker’. Such a body could also play a key role as a focal point for the clinical trials community and provide a platform for the sharing of knowledge and experience.

2.3.3 Evidence on good practice is being built, but additional data, evidence and case studies are still needed.

Although there has been great progress in the development of methods to footprint research activities, the **evidence base is still being built**. More data are needed on the emissions associated with different activities of publicly-funded and industry clinical trials and associated laboratory research, and on

[22] https://wellcome.org/what-we-do/our-work/environmental-sustainability-concordat#management-of-the-concordat-a579
[23] chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://a.storyblok.com/f/109506/x/96fc198cb8/smi-hstf-executive-summary.pdf

mitigation strategies that can help reduce clinical trial associated emissions and feed into guidance on good practice.

This evidence could take multiple forms, from formal quantitative research to case studies of innovative practice. Thought also needs to be given to effective dissemination through the clinical trials community, both of new knowledge and also examples of good practice Recognition and consideration of how to build workforce capacity is also required.

2.3.4 Guidance and harmonisation are important, but flexibility is critical in a rapidly evolving area.

Despite much recent progress, it is still early days. Consistent approaches would be valuable, and can be facilitated by the development of common methods and guidance on good practices. However, some degree of flexibility needs to be maintained so that new understanding can be incorporated as it emerges and to provide continuing scope for innovation.

There are still opportunities to **"learn by doing".** Striking the right balance between consistency and flexibility may be challenging, but a guiding principle could be to build in flexibility by design, for example by developing draft best practice but ensuring they are updated frequently. This further emphasises the need for continuing collection and sharing of data and evidence.

One potentially significant unknown is the growth of **digital and AI-based tools for clinical trials**. Emissions associated with the use of digital tools have not traditionally been given much thought, although it is generally assumed that virtual approaches are more environmentally friendly as they require less travel. However, the increasing use of AI tools, which can have enormous energy demands[24], is questioning this assumption. It is likely that increasing consideration will need to be given to the virtual collection and analysis of data, and whether it is strictly necessary for individual projects. Furthermore, virtual approaches should be optional, based on participant preferences. Barriers to virtual approaches for those who wish to engage digitally (access to devices and/or connectivity infrastructure) must be removed. Participants who prefer to digitally engage using their own devices can help keep hardware waste at low levels, but no additional financial expenses should be incurred, for example, because the local data collection and processing on own devices pushes up phone tariffs.

2.3.5 We are close to an inflexion point where clinical trial carbon emissions can be estimated routinely–where do we go from here?

A key shift will be to **mainstream carbon footprint assessments** so that they become a routine and integral part of clinical trial design and management, and used to drive changes to minimise trial-associated emissions. Footprinting tools are becoming available and become easier to use once they are familiar. The path laid by **patient and public involvement (PPI),** now a routine aspect of clinical research in the UK and some other countries, as well as the greater attention now given to research impact and equity, diversity and inclusion (EDI) issues in research, could provide important lessons on mainstreaming. Furthermore, there exists the potential to build the capacity for factoring in qualitative data on how these footprinting tools are implemented in practice. This could provide feedback on the challenges and successes of their implementation that could help drive adoption forward.

[24] https://iea.blob.core.windows.net/assets/6b2fd954-2017-408e-bf08-952fdd62118a/Electricity2024-Analysisandforecastto2026.pdf

Research sites are at different levels of maturity in their ability to integrate greener practices. Research institutions and healthcare organisations (and those that provide funding to them) need to consider how to build institutional capacity in adoption of green practices. The possible conflict between green and EDI agenda will also need to be addressed, given the risk that sites with less well developed capabilities in disadvantaged settings could be excluded from studies based on green criteria.

Although there appears to be widespread support for greener practice, individual behaviours may be impacted and existing attitudes challenged. **Behavioural science** approaches have a role to play in accelerating transitions.

A wider shift in mindset might also need to embrace more fundamental aspects of research practice, such as focusing more rigorously on the need for a research study in the first place (aligning with the **research waste** agenda[25]) and by being stricter on the scope of project. The concept of starting trial design with a focus on essential research activities can help to minimise unnecessary, 'just in case' collection of data and samples.

Given variation in capacity and knowledge, the journey to greener trials can be taken in a **stepwise fashion**, beginning with incremental gains. For example, funders could begin to incorporate questions about emissions in grant applications, which at the minimum would encourage more reflection on adoption of greener practices.

It will also be key to take a long-term view, with the understanding that on occasion the carbon footprint of a clinical trial might be a necessary (and acceptable) initial environmental cost to pay if it will result in downstream patient and environmental benefit, such as if the clinical trial develops a medication that limits patient admission to a carbon-intensive ICU.

Practices can be influenced by 'carrots and sticks' – **incentives and penalties**. Several interest holder groups could use these to wield influence. While some authorities are thinking about the carbon impacts of pharmaceuticals,[26] it is unclear whether green trial design could fall within their remit. Ethics bodies might also have a role to play in ensuring green practice or in ensuring that the drive to adopt them ensures no extra harm or burden on study participants, but again it is not clear how this might apply in practice.

[25] Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet. 2009;374(9683):86-9. doi: 10.1016/S0140-6736(09)60329-9.

[26] https://www.politico.eu/article/drug-environment-europe-plan-cut-pharma-pollution-antibiotics-industry-department-skeptical-medicine-agency/

3. Views from the Sector - Regulatory Barriers

A short landscaping exercise was designed to assess the potential regulatory barriers associated with the mitigation of clinical trial associated carbon emissions. The exercise was distributed to:

(i) Chairs and Deputy Chairs of six Operational Groups within the UK Clinical Research Collaboration Clinical Trials Unit (CTU) Network[27]

(ii) Members of the Sustainable Healthcare Coalition industry Low Carbon Clinical Trials Group (iLCCT)[28]

Exercise questions are listed in Appendix A.3

Responses were received from all six CTU Network Operational Groups and three company representatives.

Responses related to contact with regulators varied. The CTU Network has had regular meetings with named individuals at the MHRA in the past, and is keen to re-establish those meetings regarding sustainability in clinical trials. Industry responses included: contact via industry associations; contact with European Medicines Agency over marketing authorisations; via a named contact; and no contact with respect to sustainability in trials.

Issues identified in Table 2 (below) relate to uncertainties expressed by respondents around implementing potential climate mitigation solutions, due to regulatory compliance concerns.

Table 2: Uncertainties around implementing potential climate change mitigation solutions

Issues suggested by CTU Operational Groups	Issues suggested by iLCCT members
• Risk-based monitoring guidance is clear but further funding guidance needed around remote monitoring via the Electronic Health Record (recognising feasibility issues at sites with less well-developed EHR systems) • Data collection mechanisms, source data considerations, and system validation when collecting data directly from participants e.g. using wearable devices • Re-use/recyclability of devices • eConsent systems approved by MHRA for at least one CTIMP deemed low risk but further discussion needed around assumed level of risk with this solution. For example, verification of potential participant's identity	• Regulatory requirements related to expiration of materials leading to waste • Varying regulation around reprocessing of medical devices across Europe • Additional measurements required by regulators • Minimising on-site monitoring whilst maintaining data integrity • Use of local rather than central laboratories whilst maintaining data integrity • Use of local patient care hubs whilst maintaining data integrity

[27] https://ukcrc-ctu.org.uk/operations-groups/
[28] https://shcoalition.org/ilcct-the-industry-low-carbon-clinical-trials-project-for-commercial-trials/

● UKCRC Policy Group eTMF guidance not yet endorsed by regulator, issues around concerns ● Energy use mitigation as use of AI increases ● Energy use mitigation for archiving	● Trial emulation using real-world evidence whilst maintaining data integrity

4. Regulatory Document Review

In order to assess where low-carbon considerations sit in the current regulatory landscape we undertook a document review of regulations governing clinical trials in four nations (United States (US), Australia, Japan, Canada) plus the EU[29]. Regulations from these nations, together, constitute a large proportion of the global clinical trials landscape. For each nation (plus the EU) we identified relevant regulatory bodies governing clinical trials and then selected the documents pertaining to the governance of clinical trial approval, including Ethical Committees (ECs) or Institutional Review Boards (IRBs). Documents were searched with keywords to find content relating to the consideration of carbon emissions in clinical trials, or indeed its mitigation. Keywords included: 'carbon', 'greenhouse gasses' and 'GHGs' We also searched for any broader discussion of environmental considerations associated with clinical trials using the keyword 'environmental'[30]. Ultimately, mentions of border 'environmental impact' were only noted, but not considered in detail, as all failed to be relevant to the topic of this report.

4.1 Regulatory document review findings

Overall, clinical trial governance is lagging behind the growing interest in considering carbon impact assessments in the design and approval of clinical trials. Table 3 summarises the results of the document review, clearly showing that the impact of carbon is currently not considered in any way by the clinical trial regulations reviewed. There was no mention of either 'carbon' or 'GHGs' in all five constituencies' clinical trial regulations. Meanwhile, 'environmental' appeared in three constituencies, but none of these mentions were relevant to the report. The results therefore clearly show that clinical trial regulation is lagging behind the growing interest in addressing the carbon impacts of clinical trials exhibited elsewhere in this report.

Table 3: Regulatory document review results

Constituency Reviewed	Relevant Agencies	Relevant Documents	Mentions of 'carbon'	Mentions of 'GHGs'	Mentions of 'environmental'
US	• Food and Drug Administration (FDA)	• *21 CFR Part 312 - Investigational New Drug Application* • *21 CFR Part 56 - Institutional Review Boards*	• None • None	• None • None	• 'Environmental' mentioned but not relevant to report • None
Australia	• Therapeutic Goods Association (TGA)	• *Therapeutic Goods Act 1989* • *Therapeutic Goods Regulations 1990*	• None • None • None	• None • None • None	• None • 'Environmental' mentioned but not relevant to report • 'Environmental'

[29] United Kingdom clinical trial regulation was left out of this document review as the focus was on expanding the knowledge base in regards to the international community's clinical trial regulation and its approach to carbon.

[30] The keyword 'environmental' was chosen as it was deemed broad enough to capture a variety of instances of phrasing that related to carbon impact, such as 'environmental impact', 'environmental harm', and 'environmental sustainability', and a variety of other possibilities. Admittedly, this approach has shortcomings, and its possible that it might have missed more esoteric phrasings in relation to carbon impact, but we deemed the keywords used sufficiently broad for the purposes of the report.

	• National Health and Medical Research Council (NHMRC)	• *Therapeutic Goods (Medical Devices) Regulations 2002* • *National Statement on Ethical Conduct in Human Research 2023*	• None	• None	mentioned but not relevant to report • None
EU	• European Commission (EC) • European Medicines Agency (EMA)	• *Regulation (EU) No 536/2014* • *Directive 2005/28/EC*	• None • None	• None • None	• 'Environmental' mentioned but not relevant to report • None
Japan	• Ministry of Health, Labour and Welfare (MHLW) • Pharmaceuticals and Medical Devices Agency (PDMA)	• *Clinical Trials Act* • *Pharmaceutical and Medical Device (PMD) Act*	• None • None	• None • None	• None • None
Canada	• Health Canada (HC)	• Part C, Division 5 of the *Food and Drug Regulations* - 'Drugs for Clinical Trials Involving Human Subjects • *Tri-Council Policy Statement 2*	• None • None	• None • None	• None • None

4.1.1 United States

Clinical trials in the US are regulated by the Food and Drug Administration (FDA), specifically: *Title 21, Chapter 1 - Code of Federal Regulations* (CFR).

Sections relevant to clinical trials include *21 CFR Part 312 - Investigational New Drug Application* and *21 CFR Part 56 - Institutional Review Boards*.

> **21 CFR Part 312 - Investigational New Drug Application**: covers the regulations governing Investigational New Drug Applications (IND). The application is a request for authorization from the FDA to administer an investigational drug or biological product to humans[31] and is required before clinical trials can begin.

[31] https://www.cc.nih.gov/orcs/ind1.html

21 CFR Part 56 - Institutional Review Boards: covers the 'general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration'[32].

There is no mention of 'carbon' or 'GHGs' in any reviewed sections. 'Environmental' was not mentioned in *21 CFR Part 56 - Institutional Review Boards*, but was mentioned in *21 CFR Part 312 - Investigational New Drug Application*. One of the requirements for submitting an IND is the inclusion of an Environmental Assessment (EA), unless the action is categorically excluded from having to do so, though all INDs are categorically excluded as per *21 CFR Part 25 - Environmental Impact Considerations* - clause 25.31(e) because most actions are considered a class of action 'that individually or cumulatively do not significantly affect the quality of the human environment'[33]. Those submitting INDs with an EA categorical exclusion must stipulate that, to their knowledge, no extraordinary circumstances exist that would mean an action on an IND would trigger the above threshold. This essentially renders INDs exempt from submitting EAs.

4.1.2 Australia

Clinical trials in Australia are regulated by the Therapeutic Goods Association. The three pieces of legislation relating to clinical trials include:

- Therapeutic Goods Act 1989
- Therapeutic Goods Regulations 1990
- Therapeutic Goods (Medical Devices) Regulations 2002.[34]

Human Research Ethics Committees (HRECs) are primarily governed by the National Health and Medical Research Council (NHMRC), in accordance with the *National Statement on Ethical Conduct in Human Research 2023*[35].

No mention of 'carbon' or 'GHGs' is present in these documents. 'Environmental' is only mentioned in the *Therapeutic Goods Regulations 1990* and *Therapeutic Goods (Medical Devices) Regulations 2002*. In *Therapeutic Goods Regulations 1990* 'environmental' is mentioned nine times. The first three mentions specifically pertain to the handling of mercury; the next six mentions pertain to the storage, relocation, disposal, and record-keeping for "biologicals'". In *Therapeutic Goods (Medical Devices) Regulations 2002*, 'environmental impact' is mentioned six times, with all mentions pertaining to the storage, relocation, disposal, and record-keeping for medical devices.

4.1.3 European Union

The European Commission (EC) is responsible for overseeing clinical trial regulations in the EU, with the European Medicines Agency (EMA), also helping to implement the key clinical trial regulation *Regulation (EU) No 536/2014*. *Directive 2005/28/EC* lays out the standards for Good Clinical Trial Practice. Ethics Committees are devolved to the nation state level in the EU, and so were not reviewed.

[32] https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56
[33] https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-25
[34] https://www.tga.gov.au/sites/default/files/australian-clinical-trial-handbook.pdf
[35]https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2023

Neither *Regulation (EU) No 536/2014* nor *Directive 2005/28/EC* mention ‘carbon’ or ‘GHGs’. *Regulation (EU) No 536/2014* mentions ‘environmental’ once as a footnote that refers to *Directive 2001/18/EC*, a document outlining legislation around the deliberate release of Genetically Modified Organisms (GMO) into the environment.

4.1.4 Japan

Clinical trials in Japan are governed by the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PDMA). Japan introduced a new piece of clinical trial legislation in 2018, the *Clinical Trials Act*. While IRBs used to operate in a decentralized manner, since the introduction the *Clinical Trials Act*, a system of centrally regulated Certified Review Boards (CRBs) has been introduced, with specifications for CRBs listed in the Clinical Trials Act. The *Pharmaceutical and Medical Device (PMD) Act* also acts as a regulation for trials that do not fall under the *Clinical Trials Act*[36].

Neither document contained any mention of ‘carbon’, ‘GHGs’, or ‘environmental’. However, it should be noted that for the purposes of this review, english translations of the original documents were used, which may have distorted the results.

4.1.5 Canada

Clinical trials in Canada are regulated by Health Canada, who are responsible for implementing the key piece of regulation governing clinical trials in Canada, Part C, Division 5 of the *Food and Drug Regulations* - ’Drugs for Clinical Trials Involving Human Subjects’[37]. The decentralised system of Ethics Committees (typically called Research Ethics Boards (REBs)) typically adheres to the guidelines laid out in the *Tri-Council Policy Statement 2* (TCPS 2). This document is a joint policy from Canada’s three federal research agencies[38] on the ethical guidelines that should govern all research involving humans[39]. None of these documents mentioned ‘carbon’, ‘GHGs’, or ‘environmental’ in relation to clinical trials.

[36] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7160916/
[37] https://laws-lois.justice.gc.ca/eng/regulations/C.R.C.%2C_c._870/page-85.html#h-577812
[38] The Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada.
[39] https://ethics.gc.ca/eng/documents/tcps2-2022-en.pdf

5. Discussion

Climate change is having an increasingly severe impact on human health. The goal of clinical trials is ultimately to deliver benefits to people's health, and it is important that trial activities do not have unnecessary indirect impacts on health because of trial-associated contributions to carbon emissions.

In reality, trade-offs are unlikely. It is more likely that greener trial practices deliver **co-benefits** – a more sustainable health system is likely to be a better health system. However, **equity** is also an important consideration: whilst participation through digital interactions and/or remote monitoring may reduce carbon emissions, as discussed, this also raises the issue of digital exclusion.

Striking progress has been made in the development of **methods to quantify the carbon footprint of trials**. In general, there is a desire within the clinical trials community to minimise carbon emissions, and these methods will provide important tools through which this can be done, supported by the dissemination of guidance on good practice.

At the same time, it is essential that new practices do not unnecessarily **restrict or slow research** with the potential to address unmet medical needs. Adoption of consistent practices both within particular interest holder groups, such as funders and regulators, and across the trials ecosystem as a whole will help to streamline processes and maintain the efficiency of research for patient benefit. The highly international nature of much clinical research will need to be borne in mind – protocols and practices need to be standardised as much as possible, so consistency in research ethics committee and National Regulatory Authority positions is highly desirable. Research ethics committee members with experience in the carbon impacts of clinical trials will be critical. Moves to reduce emissions in research will also need to be considered alongside other factors influencing trial practice, such as participant diversity, patient engagement and decentralisation of trials.

Low-carbon objectives will also be an increasingly important consideration for the **interventions being assessed in clinical trials**. The example of the anaesthetic desflurane, the use of which has been discontinued in the NHS because of its greenhouse gas properties[40], illustrates how the environmental impact of an intervention should no longer be ignored.[41] Regulators in particular may find themselves having to incorporate sustainability assessments into product reviews, a role that could extend to encompass the design of trials and the carbon data they may be able to collect on a particular intervention.

Our document review highlighted how clinical trial regulation is currently **lagging behind** the interest in understanding and mitigating the carbon impact of clinical trials. Meanwhile, our landscaping exercise findings suggested a range of regulatory barriers impeding clinical trial carbon mitigation. To address this shortfall, carbon emissions associated with trials need to be considered by multiple groups, including sponsors, funders, ethics committees, regulators and publishers (**Table 1**). The key challenge is to determine how further progress can be made, without compromising or slowing the development of much-needed medical innovations.

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https://www.england.nhs.uk/long-read/guidance-desflurane-decommissioning-and-clinical-use/#:~:text=Considering%20the%20reduction%20of%20desflurane,routine%20practice%20by%20early%202024.

41 https://ukhealthalliance.org/news-item/health-organisations-ask-nice-to-do-more-on-environmental-issues/

Moving forward it will also be important to consider **a broader range of environmental impacts** of clinical trials beyond carbon. Difficult trade-offs may present themselves when we achieve a better understanding of the broader environmental impact of clinical trials. For example, weighing carbon impacts against land toxicity impacts or water usage may become the type of consideration that needs to be made at the outset of greener clinical trials.

In a highly dynamic environment, it will be important for the **momentum to be maintained**, with dialogue continuing across different interest holders within the clinical trials ecosystem (including the patient voice). An independent convening body could play a critical role to facilitate these conversations, bringing together the different interest holders to ensure continuing dialogue, development of shared and aligned practices, and to provide a national focal point for the greener clinical trials and medical research movement in the UK.

Role	Summary	Existing activities	Interest Holders
Advising, norms development	Identifying good practice, providing guidance, setting best practice, developing benchmarks	Funders' guidance Laboratory science accreditation schemes	Funders Regulators Academics Patient/public representatives (Special interest groups*) (Institutions)
Building capacity	Strengthening community's ability to conduct green trials	Training schemes Networks Developing communities of practice	Funders Institutions (Special interest groups)
Implementing	Following best practice	Concordat for the Environmental Sustainability of Research and Innovation Practice Sustainable Markets Initiative Health Systems Task Force	Sponsors Researchers Contract Research Organisations
Accountability	Ensuring adherence to good practice	Carbon footprint tools	Funders (e.g. through final reports) Publishers (e.g. publishing requirements) (Regulators?) Ethics Committees
Facilitating	Creating the conditions that enable green trials to be conducted	Institutional strategies/policies	Regulators NHS NHS regulators Institutions Sponsors R&D Support Networks
Coordinating	Ensuring alignment *within* and *across* interest holder groups	Sustainability concordat Greener Trials workshops UK R&D Forum	Independent convening body ('honest broker')

Educating	The academic and industry trialists designing and conducting trials need to understand how to consider the environmental impacts of trials	Training schemes	Special interest groups* Trialists

Table 1: Greener clinical trials: Possible interest holder roles

*e.g. academic networks, industry networks, CTU networks

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Appendix

A.1 Workshop agenda

Timings	Event	Speaker
8:30 - 9:00	Arrival - tea/coffee	
9:00 - 9:05	Introduction	*Prof. Paula Williamson*
9:05 - 10:15	Session 1 - Perspectives from the landscape, Q&A 1. Greener Trials - the academic trialist's perspective 2. Sustainable Trials - the industry perspective 3. Climate, Health and Sustainability in Healthcare Research - Where Greener Trials Fit in the NIHR Jigsaw 4. Reflections from patient representatives 5. Invitation for contributions from delegates, Q&A	*Chair: Dr. Gabrielle Samuel* 1. Dr. Lisa Fox - Institute of Cancer Research 2. Dr. Neil MacKillop - AstraZeneca 3. Jennifer Ekelund - National Institute of Health and Care Research 4. Amanda Roberts & Ray Gardner
10:15 - 10:30	Mid-morning refreshment break	
10:30 - 11:15	Session 2 - Breakout session	*Facilitators: Prof. Paula Williamson, Dr. Lisa Fox, Dr. Gabrielle Samuel, Matthew Graham*
11:15 - 12:00	Session 3 - Breakout group feedback & open forum discussion	*Chair: Prof. Paula Williamson*
12:00 - 12:30	Light lunch & workshop close	

A.2 Workshop contributors

Fiona Adshead	Chair, Sustainable Healthcare Coalition
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Dr. Alethea Cope	Head of Translation, Wellcome Trust
Juliet Dobson	Managing Editor, BMJ Family
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Dr. Jeff Hogg	Clinical Research Fellow, University Hospitals Birmingham NHSFT
Prof. Kerry Hood	Dean of Research & Innovation, Cardiff University
Samantha Holmes	Clinical Fellow to the Chief Sustainability Officer, BMJ
Joseph John	National GIRFT Urology Fellow, NHS England
Ian Jones	Owner, Jinja Publishing Ltd

Jason LaRoche	Director, Innovative Health, Johnson & Johnson Innovative Medicine
Addie MacGregor	Sustainability Manager, The Association of British HealthTech Industries
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Amanda Roberts	Patient Public Involvement Representative
Dr. Gabrielle Samuel	Lecturer in Environmental Justice and Health, King's College London
Sean Scott	Trustee, Research & Development Forum
Dr. Mathew Tata	Funding Policy & Governance Manager, Cancer Research UK
Prof. Paula Williamson	Professor of Medical Statistics, University of Liverpool

A.3 Landscaping exercise questions

Questions posed to the CTU Network Operational Groups and the iLCCT

(1) Do you have any contact with the MHRA about regulatory issues?

- On a regular basis, with a named contact?
- On an ad-hoc basis, with a named contact?
- On an ad hoc basis, and without a named contact?
- No

(2) Are there uncertainties around implementing potential climate mitigation solutions, due to regulatory compliance concerns? Please explain your response if you believe there is a regulatory barrier.

(i) eTMFs? Yes/No/Not sure
(ii) E-consent? Yes/No/Not sure
(iii) Moving to less on-site monitoring? Yes/No/Not sure
(iv) De-centralized patient assessments? Yes/No/Not sure
(v) Other? Please provide the detail.

(3) Please provide any further comments, concerns or suggestions you may have in relation to this topic.

Questions posed to the iLCCT

(1) Do you have any contact with the MHRA, EMA, FDA, or other international bodies, about regulatory issues in general?

- On a regular basis, with a named contact?
- On an ad-hoc basis, with a named contact?
- On an ad hoc basis, and without a named contact?
- No

(2) Are there uncertainties around implementing potential climate mitigation solutions, due to regulatory compliance concerns? Please explain your response if you believe there is a regulatory barrier.

(3) Please provide any further comments, concerns or suggestions you may have in relation to this topic.