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Final Report - Enabling lower carbon clinical trials: Development and prototype testing of a method to quantify the carbon footprint of current clinical trials to inform future lower carbon clinical trial design.

Abstract

The urgency of the climate crisis requires the attention of the biomedical research community, not least clinical trials, which involve significant greenhouse gas emissions.

As a first step, the Low Carbon Clinical Trials (LCCT) Working Group set out a strategy to reduce the emissions of clinical trials, starting with the development of a method to measure their carbon footprint (CO2e). A process map defining clinical trial core activities was produced and corresponding emission factors were sourced to convert activity data into greenhouse gas emissions.

The subsequent method was piloted by application on two CRUK-funded trials (CASPS [ISRCTN63733470] and PRIMETIME [ISRCTN41579286]). Emission factors for all trial activities were identified and used to estimate the total carbon footprint. The carbon footprint of CASPS, an international phase 2 sarcoma trial of an investigational medicinal product with 47 participants, was 72 tonnes CO2e. PRIMETIME, a UK-based phase 3 non-investigational medicinal product breast cancer trial with 1962 patients, produced 89 tonnes CO2e. Results have been submitted for publication. A further 10 clinical trials have subsequently been footprinted using the method, data collection will be complete by the end of Oct 2023, and a second publication is planned describing common hotspots and user experience of performing carbon footprinting calculations.

A guidance document defining the scope, method and assumptions has been written to allow application of the method to any clinical trial. The guidance, which is publicly available, can be used to identify carbon hotspots where alternative approaches to trial design and conduct could reduce a trial's footprint, or where methodology research is required to investigate the potential impact of interventions taken to reduce carbon emissions.

Introduction

The World Health Organization has called climate change "the single biggest health threat facing humanity today" [1]. Whilst clinical trials are critical to identifying effective and safe treatments, in line with all healthcare activities they also have a significant environmental impact. This contribution was first recognised around 15 years ago, when Ian Roberts and the Sustainable Trials Study Group concluded that "clinical trials contribute substantially to greenhouse gas emissions…. Notably through energy use in research premises and air travel" [2]. Another study conducted by Lyle et al in 2009 of 12 UK pragmatic randomised

trials, involving an average of 402 participants, showed that the average carbon emissions generated by the trials was 78.4 tonnes [3]. Multiplying this total by the 24,104 UK trials registered on ClinicalTrials.gov would estimate the emissions of UK trials to be about 1.9 million tonnes of carbon dioxide equivalent [4]. This total, which is likely a highly conservative estimate, is roughly equivalent to 7.5% of the footprint of the UK National Health Service, which itself accounts for 6% of the UK's total footprint [5,6].

However, since these papers were published, little seems to have happened to quantify and consciously reduce the carbon consumption of clinical trials, but the urgency of the threat from climate change has increased exponentially.

It is not currently possible for trialists to easily estimate the environmental impact of running a clinical trial, which limits their ability to contribute to climate change mitigation. However, there is recognition of the requirement to reduce the carbon footprint of clinical trials and practical guidance encouraging this [7].

The Sustainable Healthcare Coalition (SHC) brought together the Low Carbon Clinical Trials (LCCT) Working Group including members of the MRC-NIHR Trials Methodology Research Partnership, UK and Ireland CRC trialists (led by the ICR-CTSU and the Liverpool Clinical Trials Centre), clinicians and others, to set out a strategy to reduce the carbon footprint of clinical trials [4]. The first step to reducing the carbon footprint of a planned clinical trial is to reliably measure its potential footprint and identify carbon hotspots. Subsequently, trialists will be able to interrogate alternative trial design approaches that may reduce the carbon footprint without impacting data quality, integrity, and validity.

Through the current award [ID: NIHR135419], we have developed a method and associated guidance that can be used by trialists to carbon footprint a clinical trial to inform future lower carbon trial design [8]. The aim is for the guidance to be applied prospectively during the design phase of a trial before trial funding is secured.

Methods

The approach to developing the guidance to estimate the carbon impact of a clinical trial comprised the following:

1) The development of a process map to capture all activities of a clinical trial;

2) The development of a method to quantify the carbon footprint of all trial activities conducted specifically for the trial and which are over and above the provision of routine care, as defined in the process map;

3) Testing of the methodology with selected clinical trials to identify activity carbon hotspots and opportunities for mitigation.

1) Process mapping

To calculate the carbon footprint of any product, process or service, the whole system must be understood and established. The ICR-CTSU and UoL team extracted information from the NIHR Clinical Trials Toolkit and a series of information gathering meetings were held with

participating UKCRC registered CTUs to understand their trial portfolios and all possible activities across a variety of clinical trial designs and interventions. The output of this stage was a visual representation of a clinical trial and a list of activities considered to be core clinical trial activities.

2) Guidance development

The core trial activities were grouped into the following modules: Trial set up; CTU emissions (includes energy and heating used in research premises, trial staff commuting and statistical analysis); Trial specific meetings and travel; Treatment intervention; Data collection and exchange; Trial supplies and equipment; Trial specific patient assessments; Samples; Laboratory; and Trial close out.

The carbon footprint of a trial was calculated by multiplying activity data by emission factors. Only activities undertaken to answer the research question, over and above routine care, were included. To identify suitable emission factors for each of the activities within the system boundary, data sources including Ecoinvent version 2.2, GOV.UK GHG conversion factors, and the SHC care pathway carbon calculator were used [9,10]. The most applicable and up to date factors that are freely available for public use were selected, and all sources referenced. It is important to note that in some cases more up to date factors, or forecasted emission factors may be available, but they are subject to licensing requirements and as such are not publicly available.

Two documents were produced, a “Detailed Guidance and method to calculate the carbon footprint of a clinical trial” and a “Data collation quick guide and worksheet”. The detailed guidance defines the project scope, limitations, assumptions, emission factors and benchmark data sources, as well as detailed breakdowns of the calculations required to calculate the carbon footprint of each activity. The “Data collation quick guide and worksheet” guides users in the application of the detailed guidance by summarising the calculations in their simplest form and displaying the activity data the user is required to collect in order to complete the required calculations.

3) Testing the methodology

Although we intend for the guidance to be used prospectively at the trial design stage, in order to test the method and develop a full and comprehensive set of calculations, this guidance was retrospectively and iteratively piloted on two ICR-CTSU managed, CRUK-funded trials, CASPS and PRIMETIME. CASPS is an international phase II trial of cedirinib in the treatment of patients with alveolar soft part sarcoma. The trial enrolled 47 patients across twelve sites in the UK, Spain, and Australia and involved an internationally shipped IMP, completion and shipment of paper CRF, on site visits by the trial team for site initiation, monitoring visits and audit, additional hospital visits for patients for trial-specific assessments and provision of tissue samples. PRIMETIME is a post-operative avoidance of radiotherapy trial which recruited 1962 patients across 64 sites in the UK. The trial used electronic data capture for collection of data, data linkage with NHS routine data sources and involved shipment of tissue samples for immunohistochemistry testing and subsequent long-term sample storage.

These two trials were selected for the initial pilot because of their contrasting designs (International CTIMP vs national non-CTIMP), the trials were complete (meaning we could test the method on the entirety of a trial), and activity information was readily available.

Having identified the trial activities using the process map and guidance, activity data was gathered from the trial protocol, Site Investigator File, funding application, trial specific databases, systems and trackers, and through discussion with the trial teams. Once collated, the trial activity data was multiplied by the emission factors identified in the guidance to calculate a carbon footprint. Application to the complete trials resulted in iteration of the guidance and addition of activities not previously identified, as well as their correlating emission factors e.g. data linkage and copying images from trial-specific scans to CDs. The full calculations for CASPS and PRIMETIME can be found in the draft publication, currently undergoing peer review: https://www.researchsquare.com/article/rs-2936937/v1.

On completion of the pilot, a further 10 clinical trials were selected from the portfolios of international and UK CRC Registered Clinical Trials Units to be footprinted. The trial type and intervention were chosen to be as broad reaching and inclusive as possible to maximise the robustness of the method. The trials included in the test phase are listed below, along with a brief description of the trial. Calculations are complete and finalised for 5 of the listed trials; final data cleaning is underway for the remaining 5, anticipated to be complete by the end of October 2023. As well as collation of data on the carbon footprinting results and hotspots, qualitative data on the use and application of the method will be collated from users and included in a subsequent publication, planned for Q4 2023.

CTU	Trial Name	Description
ICR-CTSU	CASPS	An international phase II trial of cedirinib in the treatment of patients with alveolar soft part sarcoma. The trial enrolled 47 patients across twelve sites in the UK, Spain, and Australia and involved an internationally shipped IMP, completion and shipment of paper CRF, on site visits by the trial team for site initiation, monitoring visits and audit, additional hospital visits for patients for trial-specific assessments and provision of tissue samples. [Results included in pilot paper https://www.researchsquare.com/article/rs-2936937/v1]
ICR-CTSU	PRIMETIME	A post-operative avoidance of radiotherapy trial which recruited 1962 patients across 64 sites in the UK. The trial used electronic data capture for collection of data, data linkage with NHS routine data sources and involved shipment of tissue samples for immunohistochemistry testing and subsequent long-term sample storage. [Results included in pilot paper https://www.researchsquare.com/article/rs-2936937/v1]
Cardiff Centre for	The UK stand	A two-arm pragmatic multicentre cluster randomised controlled trial which aims to evaluate the effectiveness and cost-effectiveness of KiVa, a school-based anti-bullying

Trials Research	together trial	programme, in reducing bullying in schools compared to usual practice. 116 primary schools participated from four areas; North Wales, West Midlands, South East and South West England [11].
Edinburgh Clinical Trials Unit	RESTART	A prospective, open, blinded end point, parallel group randomized clinical trial that compared the effects of starting vs avoiding antiplatelet therapy after ICH. The trial recruited 537 participants at 122 hospitals in the UK [12].
Imperial Clinical Trials Unit	ON-PACE	On-PACE is a double-blind randomised trial investigating whether taking a nutritional supplement is beneficial for people with the most severe form of chronic obstructive pulmonary disease (COPD). It will recruit 96 people with COPD who use oxygen at home to take part in a 3 month long clinical trial [13].
Liverpool Clinical Trials Centre	HEAL-COVID	HElping Alleviate the Longer-term Consequences of COVID-19 (HEAL-COVID), an adaptive platform trial, aims to evaluate the impact of treatments on longer-term morbidity, mortality, re-hospitalisation, symptom burden and quality of life associated with COVID-19. The trial took place across 109 sites and randomised 1245 participants [14].
MRC Clinical Trials Unit at UCL	MAVMET	A multicentre, 48 week randomised controlled factorial trial of adding maraviroc and/or metformin for hepatic steatosis in HIV-1-infected adults on combination antiretroviral therapy. The trial took place at 6 sites across the UK and recruited 90 participants [15].
Newcastle Clinical Trials Unit	PREMISE	A multi-arm, multi-centre, non-inferiority randomised controlled trial comparing 3 minimally invasive treatments to the current gold standard operation for bladder obstruction due to enlarged prostate in the National Health Service. The planned sample size is 536 [16].
The George Institute	INTERACT3	An international, multicentre, prospective, stepped wedge, cluster randomised, blinded outcome assessed, controlled trial of a care bundle of physiological control strategies in acute intracerebral haemorrhage. The trial recruited 7064 patients from 122 hospitals in 10 countries (Chile, Brazil, China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, and Vietnam) [17].
University of Galway	EMERGE	A randomised placebo-controlled trial of the Effectiveness of MEtformin in addition to usual care in the Reduction of

		GEstational diabetes mellitus effects. Planned sample size is 550 [18].
University of Aberdeen	INTERVAL	A UK multi-centre randomised controlled trial evaluating the effectiveness and cost effectiveness of three dental recall strategies. The trial recruited 2372 participants across 50 dental practices in the UK.
xCork University Hospital, Cancer Trials Ireland	SHAMROCK	A phase II trial of Trastuzumab deruxtecan in the neoadjuvant treatment of patients with early stage HER-2 positive breast cancer which will recruit 80 patients in 5 centres in the Republic of Ireland.

Results and Conclusion

The project has successfully delivered a method and guidance that can be used by trialists to estimate the carbon footprint of a clinical trial. The current version of the detailed guidance is undergoing further iterative testing to refine and expand its application to as many different trial types and interventions as possible. Each iteration of the guidance will be made publicly available via a peer reviewed publication, and once published, will also be uploaded onto the public-facing website of the institutions leading development and the MRC-NIHR TMRP.

Development, testing and refinement of the method to carbon footprint clinical trials is only the first step towards enabling lower carbon trial design. Footprinting a much larger number of varied trials will allow identification of hotspots, which will in turn allow identification of elements of trial design and conduct amenable to lower carbon processes. The acceptability to patients and healthcare professionals, and the methodological quality of alternative approaches need to be assured. For assessment to become routine, tools and training will need to be developed and delivered. With a method now available for application, support to scale up its use by UK trialists is needed to avoid the lack of buy-in and implementation seen in previous efforts, and the assembled academic team have submitted a request to the NIHR for continued funding to support this endeavour.

The assembled team compromises a combination of operational and methodological trialists positioned within the UK Clinical Research Collaboration (UK CRC) Clinical Trials Unit Network and the MRC-NIHR Trials Methodology Research Partnership (TMRP), combined with an acquired working knowledge of clinical research life cycle analysis. They are uniquely placed to deliver the work required. Continued funding of the assembled academic team therefore provides a vehicle with the potential to facilitate operational delivery of NIHR carbon reduction strategies which do not adversely affect methodological rigour.

Dissemination

A small project grant has been awarded by the NIHR-TMRP / HRB TMRN to support some initial engagement and dissemination activities over the next 12 months. The award will

cover a total of approximately 2 months work, which will be spread across the proposed activities/funding period. The team plan to:

- Develop and deliver a free to access, live, online training session for the UK and Ireland academic trialist community, to educate the community on the environmental impact of trials and how to quantify the carbon footprint of clinical trial activities. Further develop and expand this training with a submission of an Educational Workshop for consideration by the ICTMC 2024 Educational Committee (0.2 fte for 2 months).
- Develop and share a recorded webinar that can be accessed at any time to educate the community on the environmental impact of trials and how to quantify the carbon footprint of clinical trial activities (0.2 fte for 2 months).
- Hold drop in clinics for members of the academic trialist community to ask real life, trial-specific carbon footprinting questions and get advice and support on responsible research practices. Five 2 hour sessions to be run every other month over the 12 month period
- Engage with and present within the TMRP and TMRN Working Group 3-monthly meetings to identify opportunities for the incorporation of carbon footprinting considerations and responsible research practices in trial conduct and other methods research.
- Develop an animated video, co-produced with patients, for patients. The video would describe sustainable research practices and carbon footprinting with the aim of facilitating the conversation with patients to understand their views on carbon trade off decisions relating to participation in research (0.1 fte for 12 months).

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Appendices

Draft publication of pilot results is undergoing peer review and can be found here: https://www.researchsquare.com/article/rs-2936937/v1

Conflict of interest declaration

None