Clinical Trials: Environmental assessment method

Method document

Sustainable Healthcare Coalition

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SIGNATURE PAGE

Clinical Trials: Guidance on Appraising Sustainability

Method document

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Acronyms and Abbreviations

Name	Description
AZ	AstraZeneca
CO_2e	Carbon dioxide equivalent
EMA	European Medicines Agency
ERM	Environmental Resources Management
FDA	US Food and Drug Administration
GWP	Global Warming Potentials
ICR	Institute of Cancer Research
iLCCT	Industry Low Carbon Clinical Trials group
IMP	Investigational Medicinal Product
IPCC	Intergovernmental Panel for Climate Change
ISO	International Organisation for Standardisation
J&J	Johnson & Johnson
LCA	Life Cycle Assessment
LCI	Life Cycle Inventory
LCIA	Life Cycle Impact Assessment
MHRA	Medicines and Healthcare products Regulatory Agency
SHC	Sustainable Healthcare Coalition
SMI	Sustainable Markets Initiative

FOREWORD

The climate crisis and the necessary role of healthcare, to both take action to mitigate its own contribution to climate change and to help build human resilience to its impacts, have only become more urgent in recent years. We are at a critical point for the future health of people, communities and our environment. There is an urgent need to develop more sustainable healthcare products and services, and to do so in a more sustainable way, as part of our transformation towards a low carbon economy and take a close look at the way we use resources in healthcare.

This new methodology for footprinting clinical trials addresses a significant area of environmental impact related to healthcare. Both public and private sectors are involved in delivering vital innovative medicines, devices and other interventions to meet the healthcare needs of current and future generations. These need to be tested for their efficacy and safety before they can be used with confidence but, that very testing leads to resource use and environmental emissions.

This Clinical Trials: Guidance on Appraising Sustainability Method document has been developed as the first part of a framework of guidance and tools that, taken together, we hope will form an important reference for health system stakeholders wanting to both understand and reduce the environmental impact of clinical research. It has been developed by a collaboration of health system stakeholders, including members of the Sustainable Healthcare Coalition, Pistoia Alliance and the Sustainable Markets Initiative Health Systems Task Force, and publicly-funded clinical trials units. Such collaborative approaches are key to accelerating action on sustainability across the many actors that control, influence or have an interest in driving healthcare sustainability.

A consistent methodology for quantifying the impacts of clinical research is only the first step in driving the necessary system change. There is increased prioritisation, and action, on climate change from within the sector, as health services and their supply partners, develop and implement their net zero commitments. We must all continue to show our commitment to reducing emissions, while improving clinical and societal outcomes, and meeting both national and global levels of ambition to transition to net zero and environmental sustainability. This guidance is evidence of our shared and continuing commitment to act on sustainability.

Dr Fiona Adshead
Chair, Sustainable Healthcare Coalition

1. ACKNOWLEDGMENTS

This method document has been developed by Environmental Resources Management (ERM) on behalf of the Sustainable Healthcare Coalition (SHC), as part of the programme of the Industry Low-Carbon Clinical Trials (iLCCT) group. This project was funded by Novo Nordisk A/S as part of its collaboration with the iLCCT group. The group is comprised of the following organisations.

List of iLCCT members:

- AstraZeneca (AZ);
- Institute of Cancer Research (ICR);
- Johnson & Johnson (J&J);
- Merck;
- Novartis;
- Novo Nordisk A/S;
- Pistoia Alliance;
- Roche;
- Sanofi;
- Sustainable Healthcare Coalition (SHC); and
- University of Liverpool

Convening body and technical authors:

- Convening body – Sustainable Healthcare Coalition (SHC)
- Technical authors – Environmental Resources Management (ERM)

2. INTRODUCTION

This document constitutes the method for estimating the environmental footprint of a clinical trial.

The developed method outlines how to assess the life cycle environmental footprint of a clinical trial which has either been completed, is partially complete or is under design and planning, in alignment with the International Standard for Life Cycle Assessment (LCA) (ISO14044) and the Greenhouse Gas Protocol, Product Life Cycle Accounting and Reporting Standard.

As such, the method addresses those activities associated with a defined clinical trial to be considered, along with the data (and data characteristics) required to complete a footprint assessment.

The method is structured in relation to the four phases of a life cycle assessment (LCA), as follows:

- Goal and Scope, detailed in *Section 4.1*;
- Life Cycle Inventory, detailed in *Section 4.2*;
- Life Cycle Impact Assessment, detailed in *Section 4.3*; and
- Interpretation and Reporting, detailed in *Sections 4.4* and *5*.

Within the method document, the following terminology is adopted:

- The term “shall” is used to indicate what is obligatory;
- The term “should” is used to indicate a recommendation, rather than a requirement;
- The terms “may” or “can” are used to indicate an option that is permissible;
- The term “trial” is used to refer to a clinical trial;
- The term “study” is used to refer to an estimation of the environmental footprint of a clinical trial; and
- The term “study commissioner” is used to refer to the party(ies) who require and have initiated the estimation of the environmental footprint of a clinical trial.

The normative references for, and the definition of terms used in, this document, refer to:

- ISO 14040:2006, Environmental management – Life cycle assessment – Principles and framework[1] (hereafter referred to as *ISO 14040*);
- ISO 14044:2006, Environmental management – Life cycle assessment – Requirements and guidelines[2] (hereafter referred to as *ISO 14044*);
- Greenhouse Gas Protocol, Product Life Cycle Accounting and Reporting Standard[3] (hereafter referred to as *GHG Product Standard*); and
- Sustainable Healthcare Coalition, Care Pathways: Guidance on Appraising Sustainability, Main Document[4] (hereafter referred to as *SHC CP Guidance*).

These references allow for a wider scope of clinical trial environmental footprints, according to the defined intended study application and requirements of the study commissioner – such as expanded choice of environmental impacts to be appraised and reported – whilst maintaining overall method compliance and alignment. This method is not prescriptive and therefore does not preclude the choice of further method compliance (e.g. European Commission, Product Environmental Footprint[5]), if outlined in the defined goal and scope of the study.

[1] ISO - ISO 14040:2006 - Environmental management — Life cycle assessment — Principles and framework
[2] ISO - ISO 14044:2006 - Environmental management — Life cycle assessment — Requirements and guidelines
[3] Product Standard | Greenhouse Gas Protocol (ghgprotocol.org)
[4] Sustainable Care Pathways Guidance - Sustainable Healthcare Coalition (shcoalition.org)
[5] European Platform on LCA | EPLCA (europa.eu)

2.1 DEVELOPMENT OF METHOD

This document has been developed as part of a programme undertaken by the industry low carbon clinical trials (iLCCT) initiative, in collaboration with academic organisations and the Pistoia Alliance. The iLCCT group was convened by the Sustainable Healthcare Coalition (SHC) in response to the Sustainable Markets Initiative Heath Systems Taskforce – a group with the objective of taking joint, scalable action to accelerate the delivery of net zero healthcare[6] – and containing several organisations committed to developing tools and guidelines to facilitate the decarbonisation of clinical trials conducted by industry and academia. The technical authors of this method document are Environmental Resources Management (ERM).

The key milestones and associated timelines of the method development are detailed below:

- Method initiation: Project initiated December 2022
- Method drafted: First draft of method document written by ERM in January and February 2023
- Workshops: iLCCT draft method review workshop convened March 13th, 2023
- Method consultation: Consultation period conducted from 13th April to 10th July 2023
- Method finalised: Document finalised on 13th July 2023
- Launch and release of method: November 2023

2.2 RATIONALE FOR METHOD DEVELOPMENT

As outlined in the Sustainable Markets Initiative (SMI) Health Systems Taskforce white-paper publication[7], the global healthcare industry contributes an estimated 4-5% of total global greenhouse gas emissions, of which clinical trials are expected to contribute an important component – up to 100 million tonnes of carbon dioxide equivalent (CO_2e) per year[6].

In addition, Adshead *et al*[8] estimated a total carbon consumption of 27.5 million tonnes from 350,000 registered clinical trials, further highlighting the pressing requirement to decarbonise. Adshead et al also proposed a strategy for achieving this decarbonisation – the development of calculation tools which will enable reliable calculations of total environmental impacts of clinical trials and the ability to identify particular areas of activity with a high impact-intensity (or 'hotspots') to be addressed as a priority.

This document represents the first step towards the development of these tools. Its principal aim is to provide a method to enable a more consistent quantification of the life cycle environmental impacts across all types of clinical trials undertaken globally, setting out a common reference standard for parties to use whilst footprinting a clinical trial(s) under their ownership or trial(s) in which they are partaking or have an interest in. The document is intended for use by life cycle assessment (LCA) practitioners, as it requires a level of LCA expertise and familiarity with LCA methods.

This method document will form the first part of a broader programme, which subsequently will incorporate development of a guidance document (constituting data and a step-by-step manual for their use based on this method, for clinical trial environmental footprinting) and an on-line calculation tool further to operationalise clinical trial footprinting.

[6] Health Systems taskforce | Sustainable Markets Initiative (sustainable-markets.org)
[7] The digital solution for sustainability in clinical research, Health Systems Task Force White Papers | Sustainable Markets Initiative (sustainable-markets.org)
[8] A strategy to reduce the carbon footprint of clinical trials - The Lancet

3. SCOPE OF METHOD

3.1 CLINICAL TRIAL DEFINITION

This method document provides for the assessment and reporting of the environmental footprint of a clinical trial.

For the purposes of this document, a clinical trial can be defined as **either**:

"A research study in which one or more human subjects are *prospectively assigned* to one or more *interventions* (which may include placebo or other control) to evaluate the effects of those interventions on *health-related biomedical or behavioural outcomes*[9]."

Or

"Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy[10]."

This flexibility in definition allows the environmental footprinting of the broadest scope of clinical trials. Clinical trials may be defined further with regard to their scale, or the phase of study, into Phase 1, 2, 3 or 4 trials, as detailed in the *Glossary*.

3.2 GEOGRAPHICAL SCOPE OF METHOD

This method is to be used to footprint clinical trial activities in any geographic region globally.

The method is not restricted by the geographic location of the clinical trial or trial activities, however, it is recognised that the accuracy of evaluation is dependent on the availability of country- or regionally-specific data.

[9] NIH's Definition of a Clinical Trial | grants.nih.gov

[10] ICH E6 (R2) Good clinical practice - Scientific guideline | European Medicines Agency (europa.eu)

4. METHOD FRAMEWORK FOR CLINICAL TRIALS ENVIRONMENTAL FOOTPRINTING

4.1 GOAL AND SCOPE DEFINITION

4.1.1 General

The goal and scope of any environmental footprint of clinical trials shall be clearly defined and shall be consistent with the study's intended application.

It is recognised that, due to the iterative nature of environmental footprints, the defined scope of assessment may have to be refined during the study. No additional implications are expected from this beyond a need to change the goal and scope of a study.

For further information concerning study goal and scope definition, refer to *ISO 14044, Section 4.2*.

4.1.2 Goal of the study

In defining the goal of a clinical trial environmental footprint, the following items shall be unambiguously stated:

- The study commissioner/organiser;
- The intended application of the study;
- The reasons for carrying out the study; and
- The intended audience (i.e. to whom the results of the study are intended to be communicated).

Appropriate applications may include:

- Providing a basis for environmental communication and reporting;
- Understanding impact reduction opportunities;
- Tracking and benchmarking environmental footprint; and
- Comparing trial designs.

The scope for comparison between trials is extremely limited, given the general disparity in terms of functional equivalence. The opportunity for comparison is primarily limited to improving the design of a trial or a trial programme with the same purpose and to monitoring general trends in the environmental footprints of trials and the overall contribution made by trials, for example to the footprint of an organisation.

The method on its own shall not be used to support comparative assertions between organisations. Comparative assertion requires ensuring functional equivalence and adherence with the requirements of ISO14044 with respect to comparative studies. The method should be used to improve the environmental footprint of trials within a given organisation.

4.1.3 Scope of the study

4.1.3.1 General

Within the scope of the clinical trial environmental footprint, the following items shall be considered and clearly described:

- A description of the clinical trial to be footprinted;
- The functional unit of the environmental footprint;
- The defined system boundary of the studied system, and corresponding system diagram;
- The environmental impacts to be appraised, and the selected impact methods;
- The system cut-off rules applied;

- The study data requirements and sources;
- The assumptions used in the study and its limitations;
- The allocation procedures applied, if required;
- Interpretation and reporting; and
- Assurance / critical review.

Any modifications to the defined goal and scope of an environmental footprint of clinical trials made during the study should be documented, along with a supporting justification.

For further information concerning the scope of a study, refer to *ISO 14044, Section 4.2.3*.

Some of the above items are specified in further detail in the following *Sections 4.1.3.2* to *4.1.3.10*.

4.1.3.2 Trial description

In describing the trial to be environmentally footprinted, the description should include:

- Name of the clinical trial;
- Stated purpose of trial;
- Provide links (e.g. clinicaltrials.gov) and references to trial documents in the public domain, if applicable;
- Whether the clinical trial has finished or is ongoing, or whether the environmental footprint is of the design of a new trial;
- Trial start and end date[11];
- Time period to be appraised, if different from trial start and end date;
- List of countries where trial activities occur; and
- Number of enrolled trial participants.

4.1.3.3 Functional unit of environmental footprint

The *functional unit* of an environmental footprint is defined in *ISO 14044* as the "*quantified performance of a product system for use as a reference* unit".

A primary purpose of a defined functional unit is to provide a reference to which the input and output data are normalised. This requires that the functional unit shall be clearly defined and measurable. The functional unit shall be consistent with the goal and scope of the environmental footprint (text adapted from *ISO 14044, Section 4.2.3.2*).

The functional unit for a clinical trial is *all of the trial activities conducted within the specified time period of the complete or partial trial for the stated trial purpose*.

For further detail concerning the definition and function of the study functional unit, refer to *ISO 14044, Section 4.2.3.2.*

4.1.3.4 System boundary

The system boundary determines which activities shall be included within the environmental footprint.

The selection of the studied clinical trials system boundary shall be consistent with the goal of the study and the criteria used to establish the system boundary shall be identified and explained (text adapted from *ISO*

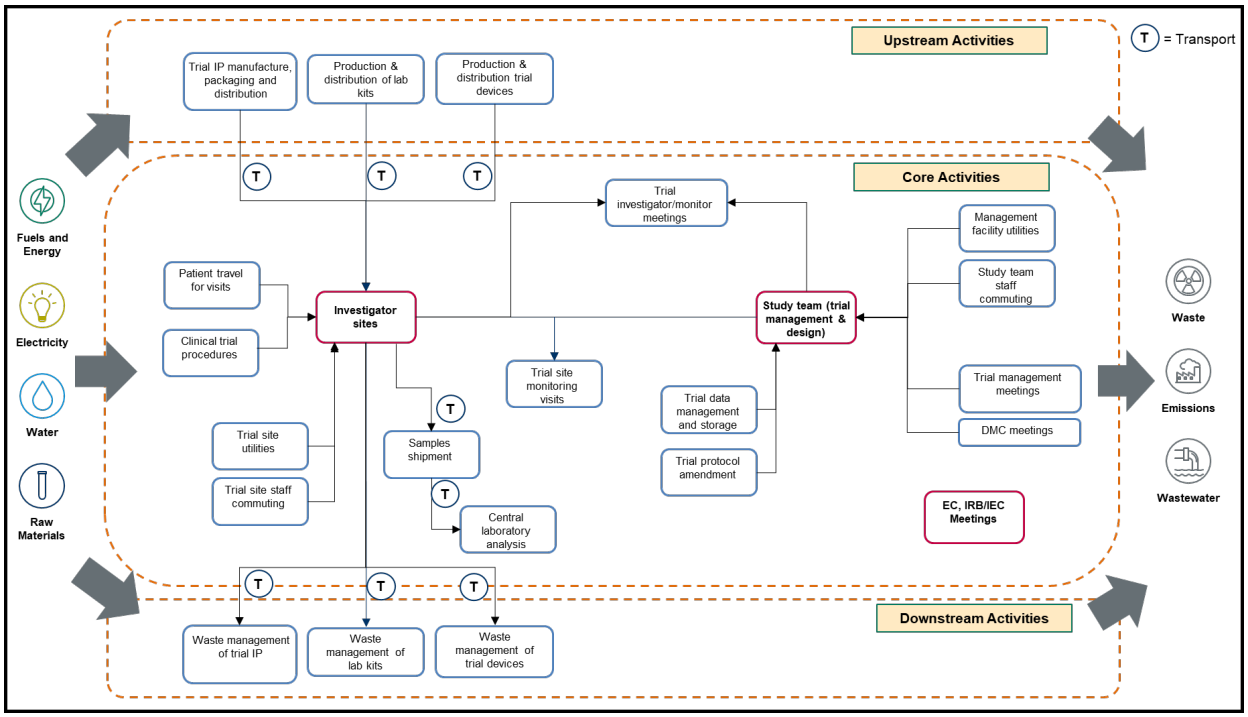
[11] It is important to note that emissions may occur from trial activities beyond the defined trial dates or time period of appraisal. These are to be included in the defined system boundary but are attributed to the activities within the stated time period.

14044, Section 4.2.3.3.1). Examples of clinical trial activities are provided in Figure 1 and Exhibit 9 of the Sustainable Markets Initiative (SMI) Health Systems Taskforce white-paper publication[12].

The clinical trial system should be modelled in such a manner that its boundaries are inputs and outputs to and from the environment or other distinct product systems not addressed within this method.

The system boundary shall be presented using a system diagram of clinical trial activities, such as the example displayed in Figure 1.

Figure 1 - System diagram of an example clinical trial



In the definition of the clinical trial system boundary to be studied, all attributable processes from cradle-to-grave should be included within the system boundary, using the principle of materiality.

The principle of materiality, as defined in the *SHC CP Guidance*, refers "*to ensuring that all activities that have a significant impact on the environmental performance results and that could influence any future decisions are included in the footprint*".

For further detail on the determination of materiality/significance, refer to the *SHC CP Guidance, Section 2.3.4* and the *GHG Product Standard, Chapter 7.3.4.*

The exclusion of clinical trial activities, processes, inputs or outputs is only permitted where it does not contravene the stated goal of the study, where the exclusion is considered to make a negligible contribution, through a materiality assessment or significance test, to the impacts being considered and its exclusion would not change the overall conclusions of the study. Any decisions to omit clinical trial activities, processes, inputs or outputs shall be clearly stated, and the reasons and implications for their omission shall be explained. Where an exclusion would materially impact on the results and conclusions of the study, the exclusion shall be tested in a sensitivity analysis (refer to Evaluation, *Section 4.4.3*).

Attributable and non-attributable processes within a clinical trials system are defined below (text adapted from *GHG Product Standard, Glossary*).

[12] The digital solution for sustainability in clinical research, Health Systems Taskforce White Papers | Sustainable Markets Initiative (sustainable-markets.org)

- Attributable processes are any flows (materials, energy, wastes) that are directly connected to the design and delivery of studied clinical trial system.
- Non–attributable processes are those that are not directly associated with the clinical trial under study and can be excluded. Examples of non-attributable processes include corporate functions such as marketing, or the construction of buildings and infrastructure.

It is important to note that for some trials, activities may be attributable and for others non-attributable either through their absence or because they represent standard of care. Attributable processes and activities for the studied clinical trial shall be appraised based on materiality.

Where activities or products are shared between separate clinical trials or other services/product systems (multi-functionality) it will be necessary to allocate between functions. For further information, refer to *Section 4.2.4*.

Attributable clinical trial activities within the system boundary are defined as either core, upstream or downstream. Examples of core, upstream and downstream activities associated with clinical trials systems are listed below and also displayed in Figure 2.

Core activities

Core activities are defined as activities which are directly related to the provision of the studied clinical trial. This includes the specific management of the clinical trial – at both a global and trial site-specific level – as well as all activities concerning direct participant engagement and delivery of the specified trial outcomes.

Example core attributable activities associated with a clinical trial, include, but are not limited to, the following:

- *Sponsor trial management & trial design*
- *Trial site(s) management*
- *Participant travel and accommodation*
- *Trial procedures (on-site & remote)*
- *Trial management meetings*
- *Assembly, packaging and distribution of trial materials between core activities e.g. to investigator sites or participants*

Where the above are associated with the provision of the studied trial these are considered to be core activities and their inclusion in the trial system boundary is required, unless they are not associated with the trial under study or are considered to be standard of care and would therefore have occurred even if the trial were not to have been undertaken.

The following are considered as part of the core activities within the clinical trial system boundary and shall be included:

- Consumptions of fuels, if combustion takes place in machinery, vehicles, offices, home-offices or other buildings such as trial sites and provided accommodation related to the core activities
- Consumptions of electricity, if use takes place in machinery, vehicles, offices, home-offices or other buildings such as trial sites and provided accommodation related to the core activities
- Consumptions of water, if consumption takes place in machinery, vehicles, offices, home-offices or other buildings such as trial sites and provided accommodation related to the core activities
- Consumptions of raw materials, if consumption takes place in machinery, vehicles, offices, home-offices or other buildings such as trial sites and provided accommodation related to the core activities
- Travel of staff (including staff commuting and travel to participants' homes), if it takes place to/from offices, or other buildings related to the study trial core activities

- Travel of participants, if it takes place to/from offices or other buildings related to the core activities
- Transport of clinical trial materials (such as IP, samples, medical devices) by air, road and sea if their use takes place in machinery, vehicles, offices, home-offices or other buildings such as trial sites and provided accommodation related to the core activities
- Solid, liquid or gaseous waste handling and treatment, if these take place in machinery, vehicles, offices, home-offices or other buildings such as trial sites and provided accommodation related to the core activities
- Emissions to environment, land, air and water (including IMP and associated metabolites), if these occur from the core activities

The following processes may be excluded from the core activities:

- Regulatory authority activities in overseeing clinical trials e.g. US Food and Drug Administration (FDA), European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA) etc.
- Maintenance of vehicles, buildings and infrastructure related to the core activities
- Construction of vehicles, buildings and infrastructure related to the core activities

Capital exclusions are justified where a core trial activity constitutes only a negligible proportion of its useful life.

Upstream activities

Example upstream attributable activities associated with a clinical trial, include, but are not limited to, the following:

- *Manufacture of trial materials:*
    - IP and placebo
    - Device manufacture
    - Samples packaging production
    - Test kits components production

The following are considered as part of the upstream activities, and shall be included:

- Consumptions of fuels, if combustion takes place in machinery, vehicles, offices or other buildings related to the upstream activities
- Consumptions of electricity, if use takes place in machinery, vehicles, offices or other buildings related to the upstream activities
- Consumptions of water, if consumption takes place in machinery, vehicles, offices or other buildings related to the upstream activities
- Production and inbound transport of raw materials, if consumption takes place in machinery, vehicles, offices or other buildings related to the upstream activities.
- Solid, liquid or gaseous waste handling and treatment, if they take place in machinery, vehicles, offices or other buildings related to the upstream activities
- Emissions to environment, land, air and water (including IMP), if these occur from the upstream activities

The following processes may be excluded from the upstream activities:

- Construction and maintenance of infrastructure/buildings related to the upstream activities
- Manufacturing of vehicles, and equipment related to the upstream activities
- Transport of staff, including commuting related to the upstream activities

Downstream activities

Example downstream attributable activities associated with a clinical trial, include, but are not limited to, the following:

- *Management of solid, liquid and gaseous wastes generated by core activities*

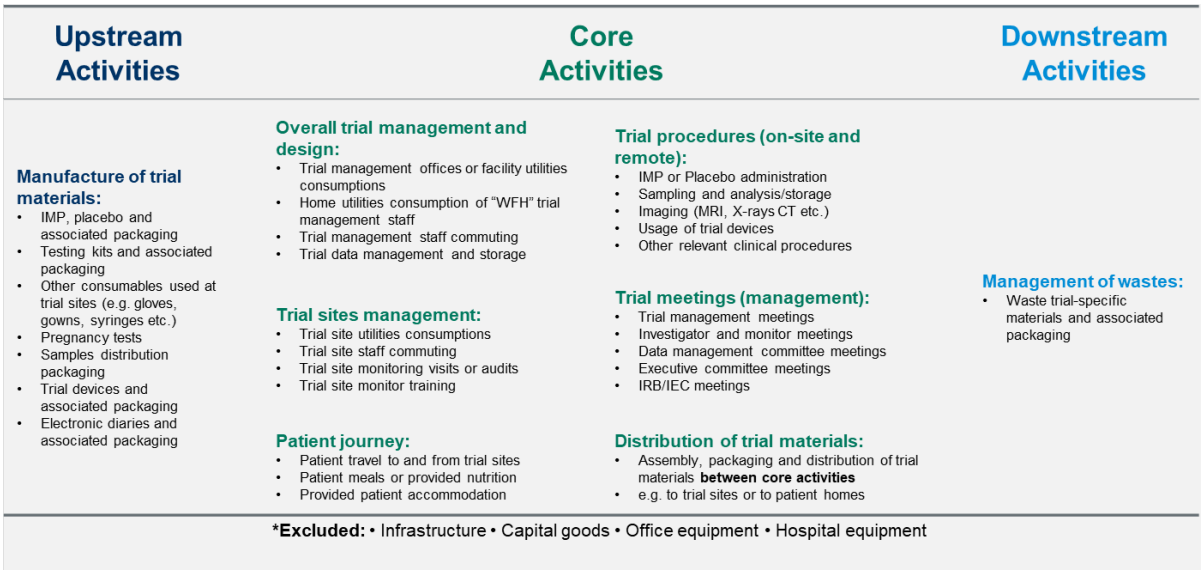
The following attributable processes are considered as part of the downstream activities, and shall be included:

- Consumptions of fuels, if combustion takes place in machinery, vehicles, offices or other buildings related to the downstream activities
- Consumptions of electricity, if use takes place in machinery, vehicles, offices or other buildings related to the downstream activities
- Consumptions of water, if consumption takes place in machinery, vehicles, offices or other buildings related to the downstream activities
- Production and inbound transport of raw materials, if their consumption takes place in machinery, vehicles, offices or other buildings related to the downstream activities
- Solid, liquid or gaseous waste handling and treatment, if it takes place in machinery, vehicles, offices or other buildings related to the downstream activities
- Emissions to environment, land, air and water (including IMP and associated metabolites), if these occur from the downstream activities

The following processes may be excluded from the downstream activities:

- End of life management of vehicles related to the downstream activities
- End of life management of infrastructure/buildings related to the downstream activities
- End of life management of machinery related to the downstream activities
- Transport of staff, including commute, related to the downstream activities

Figure 2 - Example clinical trial activities



For further details concerning environmental assessment system boundaries and their definition, refer to *ISO 14044, Section 4.2.3.3*.

4.1.3.5 Impacts to be appraised, and impact methods used

The environmental footprint should, as a minimum, assess greenhouse gas emissions expressed as the sum of the global warming potential, on a 100-year timeframe, using global warming potentials (GWP) from the latest IPCC report. The sum of the GWP should be expressed in either kg CO_2e or tonnes CO_2e.

The global warming potential (GWP) is a metric used to calculate the cumulative radiative forcing impact of multiple greenhouse gases (GHGs) in a comparable way. Companies should use GWP values from the Intergovernmental Panel for Climate Change (IPCC) Sixth Assessment Report[13], published in 2021, or the most recent IPCC values when the Sixth Assessment Report is no longer current (text adapted from *GHG Product Standard, Section 11.2*).

The source of GWP values and the time scale shall be clearly stated when reporting CO_2e results.

The requirement to assess global warming potential using the latest IPCC GWP characterisation factors does not preclude the application of additional climate change impact methods, in line with the goal and scope.

The selection of other impact categories, category indicators and characterisation models shall be consistent with the defined goal of the study.

Examples of additional impact categories which may be selected for appraisal, and their impact methods can be found in:

- ISO/TR 14047:2012[14], *Section 3.2.1.2, Table 7*; and
- European Commission, Product Environmental Footprint Method[15], Annexes 1 & 2, *Section 3.2.3, Table 2.*

The impacts to be appraised and the methods employed shall be clearly stated.

For further guidance concerning the selection of impacts to be appraised and impact methods, refer to *ISO 14044, Section 4.4.2.2*.

4.1.3.6 Cut-off rules

Throughout the defined clinical trials system boundary, there may be inputs or outputs that are deemed to be immaterial to the results of the environmental footprint, which may be *cut-off* from the assessment in order to aid simplicity of data collection and calculations.

Typical cut-off criteria in environmental performance analysis of a clinical trial may include:

- **Mass:** only including in the study all inputs that cumulatively contribute more than a defined percentage to the mass input of the clinical trial system being modelled;
- **Energy**: only including in the study all inputs that cumulatively contribute more than a defined percentage to the energy inputs of the clinical trial system being modelled;
- **Clinical trial staff time:** only including in the study all inputs that cumulatively contribute more than a defined percentage to the trial staff time of the clinical trial system being modelled; and
- **Environmental significance:** only including in the study elementary flows to and from the clinical trial system that contribute more than a defined percentage of the estimated total impact, for each environmental impact to be assessed.

The cut-off criteria applied within the clinical trials environmental footprint, as well as the assumptions upon which the selected criteria are established, shall be clearly described. The effect on the outcome of the study due to the selection and application of cut-off criteria should also be assessed and documented.

[13] Climate Change 2021: The Physical Science Basis | Climate Change 2021: The Physical Science Basis (ipcc.ch), Chapter 7
[14] ISO - ISO/TR 14047:2012 - Environmental management — Life cycle assessment — Illustrative examples on how to apply ISO 14044 to impact assessment situations
[15] Recommendation on the use of Environmental Footprint methods (europa.eu)

The practical application of cut-off criteria requires consideration of the likely scale of a flow in comparison with a known flow associated with the trial under study.

For further detail concerning the selection and application of cut-off criteria, refer to *ISO 14044, Section 4.2.3.3.3.*

4.1.3.7 Types and sources of required data

The data selected and required for an environmental footprint of a clinical trials system will depend on the defined goal and scope of the assessment.

The environmental impacts to be appraised will determine the flows to and from the environment to be quantified for the core, upstream and downstream processes.

In general, an environmental footprint requires two types of information/data:

- Process activity data relating to the activities within the studied clinical trial system.
    - Data may include materials, energy, direct emissions or waste flows from, into or between clinical trial activities/processes.
    - The commissioner/organiser of the study is responsible for providing data for the activities under their control. For the other core activities, upstream and downstream activities data are ideally provided by the owner of these activities. However, in practice some or most of these data may need to be based on the commissioner's appreciation of the scale of activity that occurs and/or secondary data (e.g. from literature, previous studies, clinical trial databases etc.).
    - These data shall be as specific as possible and shall be representative of the clinical trial system under study.
- Life Cycle Inventory (LCI) data relating to the flows to and from the environment and other product systems that relate to the activity data.
    - These data are usually drawn from life cycle inventory databases (such as ecoinvent[16]) or other published emission factors when addressing specific impacts such as climate change.

Data requirements should consider the desired accuracy and precision of results, to be aligned with the defined goal and scope of the study.

Data sourced or collected relating to the studied clinical trial system activities/processes are classified into either *primary* data, *secondary* data and *proxy* data as defined below (text adapted from *GHG Product Standard, Glossary*):

Primary data: data from specific activity/processes in the studied clinical trial;

Secondary data: process data that are not from the specific activity/processes in the studied clinical trial; and

Proxy data: data from a similar activity that are used as a substitute for the given trial activity. Proxy data can be extrapolated, scaled up, or customized better to represent the required trial activity.

4.1.3.8 Rules for electricity

As with other sources of secondary data, it is preferable to select data that are geographically representative of the trial. The preference is to use supplier specific data where the potential for double-counting is avoided through contractual arrangements and the availability of the related residual grid factors. Where there is doubt, regional average LCI data for electricity should be used.

The electricity LCI/emission factor data used and the basis for appraising electricity shall be documented.

[16] Home - ecoinvent

4.1.3.9 Data quality assessment and requirements

During the collection of data (both process activity and LCI data) to be used in the environmental footprint of a clinical trial system, attention shall be paid to the quality of these data.

Assessing and understanding the quality of data used in an environmental footprint will:

- Enable overall improvement of data quality in the study inventory;
- Assist in a study's assurance process, if required; and
- Demonstrate the quality of inventory data to stakeholders and third-parties.

When selecting data, consideration of the following is required (text taken from *ISO14044, Section 4.2.3.6*):

- Time-related coverage of data;
- Geographical coverage of data;
- Technology coverage of data;
- Precision of data;
- Completeness of data;
- Representativeness of data;
- Consistency of data;
- Reproducibility of data;
- Sources of data; and
- Uncertainty of data.

For further details, refer to *ISO 14044, Section 4.2.3.6.*

As a minimum, a qualitative data quality assessment appraising the following five data quality indicators shall be completed (text taken and modified from *GHG Product Standard, Section 8.3.7*):

- *Technological representativeness*: the degree to which the data reflect the actual technology(ies) used;
- *Temporal representativeness*: the degree to which the data reflect the actual time (e.g. year) or age of the activity;
- *Geographical representativeness*: the degree to which the data reflect the actual geographic location of the activity (e.g. country or site);
- *Completeness*: the degree to which the data are statistically representative of the relevant activity; and
- *Reliability*: the degree to which the sources, data collection methods and verification procedures used to obtain the data are dependable.

Further information concerning assessment of data quality and scoring criteria for performing a qualitative data quality assessment can be found in the *GHG Product Standard, Section 8.3.7.*

Semi-quantitative data quality assessments

Semi-quantitative data quality assessments (e.g., data quality assessment requirements of the European Commission, Product Environmental Footprint Method[17], outlined in *Annexes 1 & 2, Section 4.6.5.*) of collected data are recommended when aligned with the goal and scope of the study.

4.1.3.10 Assurance / critical review

The goal and scope of the clinical trials environmental footprint shall define the following:

- If a critical review and assurance of the footprint is required or necessary;
- What type of critical review (internal, external, panel) and assurance (first, third party) would be required;
- If required, how to conduct the review and the level of assurance (limited, reasonable); and
- Who will conduct the critical review and provide assurance, what are their credentials and level of expertise.

For further details concerning the definition of critical review and assurance considerations, refer to *ISO 14044, Section 4.2.3.8. and the GHG Product Standard, Section 12*.

4.2 LIFE CYCLE INVENTORY ANALYSIS (LCI)

4.2.1 General

The defined goal and scope of the clinical trial's environmental footprint provides the initial plan for collecting and calculating, where required, data in order to conduct the life cycle inventory phase of an LCA.

The life cycle inventory quantifies the energy and raw materials used, the emissions to atmosphere, water and soil, and the wastes associated with each trial activity (upstream, core and downstream) and the product systems they utilise (e.g. electricity, fuel, material used by each clinical trial activity) from cradle to grave, relative to the functional unit.

For further details concerning life cycle inventory analysis, refer to *ISO 14044, Section 4.3.*

4.2.2 Collecting data

The qualitative and quantitative data for inclusion in the studied clinical trial inventory shall be collected for each process that is included within the system boundary (text adapted from *ISO 14044, Section 4.3.2.)*.

Primary data shall be collected for all processes under the ownership or control of the study commissioner.

The collected data, whether *primary*, *secondary* or *proxy* are used to quantify the inputs and outputs of a unit process.

The source for data collected, whether primary, secondary or proxy data, shall be stated and referenced.

Any limitations associated with the quality of data which may be significant to the conclusions of the environmental footprint shall be documented. Data quality assessments and requirements are described in *Section 4.1.3.9.*

Although it is recommended that inventory data are sourced that describe each clinical trial activity (at the level of flows to and from other activities and emissions to and resource extracted from the environment), it is accepted that some secondary and proxy data may be in the form of impact indicator emission factors e.g. kg CO_2e/unit of activity. Where this is the case, the indicator emission factors shall align with the goal and scope of the study and any limitations associated with the data be recorded and captured through the data quality assessment.

For further details concerning collecting data, refer to *ISO 14044, Section 4.3.2.*

[17] Recommendation on the use of Environmental Footprint methods (europa.eu), Annexes 1 & 2, Section 4.6.5.

4.2.3 Calculating data

4.2.3.1 General

It may be necessary to perform additional calculations on collected data.

All calculation procedures shall be explicitly documented and the assumptions made shall be clearly stated and explained. The same calculation procedures should be consistently applied throughout the study (text taken from *ISO 14044, Section 4.3.3.1).*

The following sections provide more information on the types of data calculations which may be required, such as data validation, relation of data to study functional unit, system boundary refinement and allocation.

For further details concerning data calculations, refer to *ISO 14044, Section 4.3.3.*

4.2.3.2 Validation of data

Data collected during the environmental footprint of a clinical trial may be checked for validity in order to confirm if the data quality requirements have been met.

Validity checks may involve, for example, mass and energy balances, as each unit process within the clinical trial system shall obey the laws of mass and energy conservation (e.g. the combined mass or energy inputs of a unit process must be equal to the combined energy or mass outputs, as export to another process, product system or as waste).

Obvious anomalies in collected data identified as a result of these validity checks shall require alternative data to be sourced.

For further details concerning validation of data, refer to *ISO 14044, Section 4.3.3.2*.

4.2.3.3 Relating data to unit process and functional unit

In the environmental footprint of a clinical trial, the defined functional unit is composed of multiple unit processes.

Each unit process shall be determined by an appropriate flow (such as a defined amount of IMP manufactured), and the quantitative inputs and outputs required for the unit process shall be calculated in relation to this flow.

As defined by the studied clinical trial process flow map, the flows of all unit processes are related to the reference flow. As a result, the sum of all unit processes inputs and outputs (the system inputs and outputs) will be referenced to the functional unit of the environmental footprint.

For further details concerning relating data to unit processes or functional units, refer to *ISO 14044, Section 4.3.3.3*.

4.2.3.4 Refining the study system boundary

As the environmental footprint is performed, decisions concerning the inclusion or exclusion of data may need to be taken. These shall be taken based on a sensitivity analysis to determine their significance.

As required, the initial clinical trial system boundary shall be revised according to the cut-off rules defined in the study goal and scope and through materiality assessment. This process shall be documented.

This refinement process may result in (text adapted from *ISO 14044, Section 4.3.3.4):*

- An exclusion of clinical trial activities, or unit processes, when a lack of significance can be demonstrated (according to defined cut-off criteria);
- An exclusion of inputs or outputs to the clinical trial system, according to significance; and
- An inclusion of clinical trial activities, unit process, system inputs or outputs that are now shown to be significant.

This data analysis is intended to allow ease of data handling and performance of the environmental footprint.

For further details concerning system boundary refinement, refer to *ISO 14044, Section 4.3.3.4.*

4.2.4 Allocation

4.2.4.1 Multi-functionality

Within the studied clinical trials system, there may be processes and activities which share inputs and outputs with another separate clinical trial, other healthcare activities or other product systems.

Allocation refers to the process of distributing shared activities or resources between different systems, or unit processes. Allocation is defined in *ISO 14040* as: "*partitioning the input or output flows of a process or a product system between the product system under study and one or more other product systems".*

For example, sourcing aggregated electricity consumption data from multi-purpose clinical trial sites where multiple, distinct clinical trials or healthcare services may be being conducted simultaneously.

For further details concerning allocation, refer to *ISO 14044, Section 4.3.4*.

4.2.4.2 Allocation procedure

The allocation procedures outlined in *ISO 14044, Section 4.3.4.2*. shall be followed when input or output data are required to be allocated to the clinical trial system under study.

Where possible, allocation shall be avoided. However, it is acknowledged that in many cases the types of data available necessitate allocation (an example being aggregated utilities consumption data at facilities and trial sites).

Where allocation is required, allocation based on physical relationships between the unit process or systems under consideration is preferred. If this is not possible, other allocation methods may be used, such as those based on service costs or economic value. All decisions regarding allocation methods selected shall be documented.

When determining the allocation approach, a key consideration is which variable is most significant for determining the level of activity. For example, is there a strong relationship between consumption of electricity within a clinical trial site and floor space, number of staff, length of procedures or total number of procedures completed. (text adapted from *SHC CP Guidance, Section 2.3.5*).

Examples of relationships which may be used to allocate between activities or systems include, but are not limited to, the following:

- Floor space (e.g. the area within a multi-trial facility which is directly related to the clinical trial system under study);
- Relative intensity (e.g. the number of participants or staff required for the clinical trial system under study); and
- Time (e.g. the time required to conduct the clinical trial system under study).

For further details concerning allocation procedure, refer to *ISO 14044, Section 4.3.4.2*.

4.2.4.3 Allocation procedure for recycling and reuse

Addressing the use of recycled materials (or recovered energy) or the recycling of wastes (recovery of energy), generated by clinical trial activities and the subsequent use by a different clinical trial or product system generally requires rules on how to account for, or apportion, impact between product systems.

For simplicity, the recycled content method is recommended. The user of the recycled material or recovered energy from waste incurs the burden of producing/recovering the recycled material/energy, and the source of the waste incurs the transport of that waste. Where an alternative allocation method is employed for dealing with the use of recycled material or the management of waste by recycling, it shall be justified and

documented. Where the selection of alternative allocation approaches would materially impact on the results and conclusions of the study, alternative allocation approaches shall be tested in a sensitivity analysis.

For reuse, similar complexities arise. For simplicity, it is recommended that reuse is treated the same as recycling. The original purchaser of the new product incurs the full manufacturing impact and the subsequent disposal impact for the proportion of the product which is not reused. The user of refurbished products incurs the refurbishment impact. The burden of transportation to recycling/refurbishment is attributed to the original user. Where an alternative allocation method is employed for dealing with reuse it shall be justified and documented. Where the selection of alternative allocation approaches would materially impact on the results and conclusions of the study, alternative allocation approaches shall be tested in a sensitivity analysis.

For further details concerning allocation procedure for recycling and reuse, refer to *ISO 14044, Section 4.3.4.3.*

4.3 LIFE CYCLE IMPACT ASSESSMENT (LCIA)

4.3.1 LCIA mandatory steps (classification and characterisation)

The approach to life cycle impact assessment (LCIA) calculation is defined by the goal and scope of the study, in terms of the selected environmental impact categories and impact indicators under consideration.

LCIA calculates the potential effects of the resource use and emissions determined in the inventory analysis of a clinical trial to each of the impact category indicators selected to be appraised.

The first stage is to identify the environmental flows that contribute to each impact, called classification. Flows may contribute to more than one impact category indicator. The second stage is to quantify the potential contribution of each flow to each impact category indicator using characterisation factors. This is called characterisation.

Characterisation factor: a factor derived from a characterisation model which is applied to convert an assigned life cycle inventory analysis result to the common unit of the category indicator (e.g. kg CO_2e / kg of gas).

When considering climate change and the GWP indicator, the assessment shall apply the GWP 100-year timescale values from the Intergovernmental Panel for Climate Change (IPCC) Sixth Assessment Report[18], published in 2021, or the most recent IPCC values when the Sixth Assessment Report is no longer current, to the greenhouse gas emissions and removals for the clinical trial system.

The method and assumptions, if relevant, used in calculating indicator results for the different environmental categories shall be documented.

If the environmental footprint of a clinical trials system is considering **multiple environmental impacts including climate change**, the LCIA calculation steps outlined in the ISO 14044 standard for life cycle assessment should be followed.

These can be found in *ISO 14044, Section 4.4*.

Other than a requirement to include an assessment of global warming potential in conformance with the GHG Protocol, this method does not prescribe which other impact indicators are to be appraised. Nor does it restrict the appraisal of other indicators for climate change.

It is recommended that a wide range of impacts and indicators are considered. They should address both the range and significance of impacts to which clinical trials contribute, so as to avoid the potential for burden-shifting. However, it is appreciated that the current priority for the clinical trials sector is addressing its contribution to climate change. In a European context, and if aligned with the stated goal and scope of the study, users of this method may look to the European Commission Product Environmental Footprint Method for instruction[19] on other impact indicator methods to be appraised.

[18] Climate Change 2021: The Physical Science Basis | Climate Change 2021: The Physical Science Basis (ipcc.ch), Chapter 7

[19] Recommendation on the use of Environmental Footprint methods (europa.eu)

For further details concerning the assignment of LCI results to the selected impact categories, refer to *ISO 14044, Section 4.4,* which should be consulted for additional guidance.

4.3.2 Optional elements of LCIA

In addition to the required elements of LCIA set out above, and if specified in the study goal and scope, the following optional elements may be used and reported separately to the calculated indicators results:

- **Normalisation** (calculating the magnitude of category indicator results relative to reference information);
- **Grouping** (sorting and possibly ranking of the impact categories); and
- **Weighting** (converting and possibly aggregating indicator results across impact categories using numerical factors based on value-choices).

For further detail concerning the optional elements of LCIA, refer to *ISO 14044, Section 4.4.3*, which should be consulted for further guidance.

4.3.3 LCIA results

For each impact indicator, the contribution from each clinical trial activity shall be tabulated and organised into upstream, core and downstream activities with sub-totals for each and a total impact indicator in relation to the functional unit. The contribution of each activity should also be calculated as a percentage of the total.

Checks should be undertaken to ensure indicator results reflect the scale of the inventory flows and the correct characterisation factor is applied.

4.4 LIFE CYCLE INTERPRETATION

4.4.1 General

The interpretation of an environmental footprint of a clinical trial system should contain the following elements (text taken from *ISO 14044, Section 4.5.1):*

- **Identification of the significant issues** based on the results of the LCI and LCIA phases;
- An **evaluation** that considers completeness, sensitivity and consistency checks; and
- **Conclusions, limitations, and recommendations**.

In general, the goal and scope and interpretation stages of an assessment shall be used to frame the study, with the LCI and LCIA stages producing information relating to the studied clinical trial system.

This means that the results of the LCI and LCIA shall be interpreted according to the defined goal and scope.

The interpretation of results shall include an assessment of significant inputs and outputs to the clinical trial system and methodological choices to understand the innate uncertainty of the results.

For further detail concerning the life cycle interpretation stage, refer to *ISO 14044, Section 4.5.*

4.4.2 Identification of significant issues

The identification of significant issues in the context of the stated goal of the study, shall structure the results from the LCIA and LCI stages of the environmental assessment.

Examples of significant issues may include:

- Key assumptions and limitations;
- Allocation;
- Data gaps; and

- Significant sources of impact (i.e. hotspot clinical trial activities) and their LCI drivers (e.g. electricity use at investigator sites).

For further detail concerning the identification of significant issues raised within an environmental footprint of a clinical trials system, refer to *ISO14044, Section 4.5.2.*

4.4.3 Evaluation

The objectives of evaluation are to establish confidence in the LCIA and LCI results of the study in meeting the stated goal of the study.

Three evaluation techniques shall be considered:

- ***Completeness check***
    - Inventory data meet the specified goal and scope data requirements
    - Inventory data allow the impact indicators to be calculated for each trial activity
    - The results calculated and sensitivity analysis are sufficient to allow interpretation in line with the stated goal and scope
- ***Sensitivity check***
    - Test alternative allocation approaches (multifunctionality, reuse, recycling)
    - Test significance and uncertainty of assumptions
    - Re-appraise justification for any exclusions
- ***Consistency check***
    - Secondary data, value judgements, assumptions, calculation methods are consistently applied and align with the goal and scope

For further details concerning data evaluation, refer to *ISO14044, Section 4.5.3.*

4.4.4 Conclusions, limitations, and recommendations

The final stage of the interpretation process in the environmental footprint of a clinical trial system is the drawing of conclusions, identification of limitations and proposal of recommendations to the intended audience of the study.

Conclusions should be drawn iteratively from the study, along with the other stages of the evaluation process outlined above. An example sequence leading to the drawing of full conclusions may resemble the following:

1) Significant issues are identified;
2) The underlying method is evaluated and the results are checked for completeness, sensitivity and consistency;
3) Preliminary conclusions are drawn, which are then checked for consistency with the defined study goal and scope; and
4) If the above steps are satisfied, the preliminary conclusions are reported as full conclusions from the study.

Recommendations shall be made based on the full conclusions reported in the study and shall reflect logical and reasonable consequences.

For further details concerning the drawing of conclusions, limitations and recommendations from a clinical trials environmental footprint, refer to *ISO 14044, Section 4.5.4.*

5. REPORTING

5.1 GENERAL REQUIREMENTS AND CONSIDERATIONS

The final stage in the conduction of an environmental footprint of a clinical trial system is the reporting and communication of the study's findings to the intended audience.

The report generated for an environmental footprint of a clinical trial system shall clearly and accurately present study results, as well as other critical information to the intended audience of the study without bias.

Critical information should include the data, methods and assumptions used in the study, as well as any identified limitations. This information should be presented transparently in a way which allows easy comprehension.

The specific requirements a study report shall be determined by the goal and scope of the study, the impact categories selected for analysis and the choice of further method compliance (in addition to this document), if relevant.

For external communication, if the study has appraised **only** the climate change impact category, the study reporting should be in compliance with the guidelines detailed in the GHG Protocol Product Standard (refer to *GHG Product Standard, Section 13*).

If the study has appraised **multiple** impact categories, then the reporting shall be in compliance with the ISO 14044 standard for life cycle assessment (refer to *ISO 14044, Section 5*). When results of the environmental footprint of a clinical trial are to be communicated to any third party regardless of the form of communication, a third-party report shall be prepared (refer to *ISO 14044, Section 5.2).*

When reporting a clinical trial environmental assessment, the study results shall be presented with a breakdown of total calculated environmental indicators into the defined upstream, core and downstream clinical trial activities for the stated functional unit.

Furthermore, a contribution analysis of each environmental impact investigated shall be presented by clinical trial activity.

Generally, the report of a clinical trial environmental performance is suggested to contain transparent documentation concerning, but not limited to, the following:

- The studied clinical trial name and description;
- The commissioner of the study;
- The stated goal of the study;
- The functional unit of the study (whether partial, complete or design of trial footprinted);
- The defined system boundary diagram and timeframe of the clinical trial system studied;
- Key assumptions used in the study;
- Results of the study;
- Sensitivity analysis;
- Conclusions and recommendations from the study; and

Assurance/critical review, if relevant or required.

6. REFERENCES

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APPENDIX A GLOSSARY OF TERMS

Glossary of terms

Allocation – partitioning the input or output flows of a process or a product system between the product system under study and one or more other product systems.

Attributable processes – refer to any flows (materials, energy, wastes) that are directly connected to the design and delivery of studied clinical trial system.

Characterisation factor – a factor derived from a characterisation model which is applied to convert an assigned life cycle inventory analysis result to the common unit of the category indicator (e.g. kg CO_2e / kg of gas).

Clinical trial – a research study in which one or more human participants are *prospectively assigned* to one or more *interventions* (which may include placebo or other control) to evaluate the effects of those interventions on *health-related biomedical or behavioural outcomes*.

Functional unit – quantified performance of a product system for use as a reference unit.

Impact category – class representing environmental issues of concern to which life cycle inventory analysis results may be assigned (e.g. climate change).

Impact category indicator – quantifiable representation of an impact category (e.g. infrared radiative forcing, W / m^2).

Non-attributable processes – are those that are not directly associated with the clinical trial under study can be excluded. Examples of non-attributable processes include corporate functions such as marketing, or the construction of buildings and infrastructure.

Phase 1 (I) clinical trial – a phase I clinical trial tests the safety, side effects, best dose, and timing of a new treatment. It may also test the best way to give a new treatment (for example, by mouth, infusion into a vein, or injection) and how the treatment affects the body. Phase I clinical trials usually include only a small number of participants who have not been helped by other treatments.

Phase 2 (II) clinical trial – a study that tests whether a new treatment works for a certain type of cancer or other disease (for example, whether it shrinks a tumour or improves blood test results). Phase 2 clinical trials may also provide more information about the safety of the new treatment and how the treatment affects the body.

Phase 3 (III) clinical trial – a study that tests the safety and how well a new treatment works compared with a standard treatment. For example, Phase 3 clinical trials may compare which group of participants has better survival rates or fewer side effects. In most cases, treatments move into Phase 3 clinical trials only after they meet the goals of Phase 1 and Phase 2 clinical trials. Phase 3 clinical trials may include hundreds of people.

Phase 4 (IV) clinical trial – a type of clinical trial that studies the side effects caused over time by a new treatment after it has been approved and is on the market. These trials look for side effects that were not seen in earlier trials and may also study how well a new treatment works over a long period of time. Phase 4 clinical trials may include thousands of people.

Primary data – data from specific activity/processes in the studied clinical trial.

Principle of materiality – ensuring that all activities that have a significant impact on the environmental performance results and that could influence any future decisions are included in the footprint.

Proxy data – data from a similar activity, that are used as a stand-in for the given trial activity. Proxy data can be extrapolated, scaled up, or customized to better represent the required trial activity.

Secondary data – process data that are not from the specific activity/processes in the studied clinical trial.