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# Reducing the environmental impact of surgery on a global scale: systematic review and co-prioritization with healthcare workers in 132 countries

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## Abstract

**Background:** Healthcare cannot achieve net-zero carbon without addressing operating theatres. The aim of this study was to prioritize feasible interventions to reduce the environmental impact of operating theatres.

**Methods:** This study adopted a four-phase Delphi consensus co-prioritization methodology. In phase 1, a systematic review of published interventions and global consultation of perioperative healthcare professionals were used to longlist interventions. In phase 2, iterative thematic analysis consolidated comparable interventions into a shortlist. In phase 3, the shortlist was co-prioritized based on patient and clinician views on acceptability, feasibility, and safety. In phase 4, ranked lists of interventions were presented by their relevance to high-income countries and low–middle-income countries.

**Results:** In phase 1, 43 interventions were identified, which had low uptake in practice according to 3042 professionals globally. In phase 2, a shortlist of 15 intervention domains was generated. In phase 3, interventions were deemed acceptable for more than 90 per cent of patients except for reducing general anaesthesia (84 per cent) and re-sterilization of ‘single-use’ consumables (86 per cent). In phase 4, the top three shortlisted interventions for high-income countries were: introducing recycling; reducing use of anaesthetic gases; and appropriate clinical waste processing. In phase 4, the top three shortlisted interventions for low–middle-income countries were: introducing reusable surgical devices; reducing use of consumables; and reducing the use of general anaesthesia.

**Conclusion:** This is a step toward environmentally sustainable operating environments with actionable interventions applicable to both high- and low–middle-income countries.

## Introduction

The global climate is rapidly changing, and urgent action is needed to mitigate against the deleterious effects to health. Healthcare contributes 4.9 per cent to the world’s carbon emissions<sup>1</sup>, which is more than aviation (1.9–2.4 per cent) or shipping (1.7 per cent)<sup>2–4</sup>. Health systems cannot achieve net zero without addressing operating theatres, which are the most resource-intensive areas of hospitals<sup>5</sup>. To prevent catastrophic global warming, governments around the world have committed to ambitious net-zero goals in all sectors, including healthcare<sup>1</sup>. However, hospitals cannot achieve this without addressing operating theatres.

Trying to change a whole hospital at once is very complex and likely to fail, so operating theatres are the best place to start a journey to net-zero healthcare<sup>6</sup>. They are sheltered environments with few external influences, treat a single patient at once, involve members across a multidisciplinary team, and have a huge environmental impact<sup>7</sup>. If evidence was provided and behaviour changed in operating theatres, learning could be expanded across other hospital areas and along the patient-care pathway, from primary care to postoperative recovery. As surgical services are likely to expand to address

post-coronavirus disease (COVID) backlogs<sup>8</sup>, measures to mitigate against increased environmental impact are a priority.

Candidate interventions need to be scalable across multiple, heterogeneous hospitals, and not be limited to enthusiastic, single-centre advocates. Furthermore, they should be holistic to whole systems across the operating theatre, to prevent siloed approaches<sup>9</sup>. Interventions must not erode the safety and quality of surgical services and should be acceptable to patients<sup>10</sup>. The aim of this co-prioritization process was to generate a ranked list of globally relevant, feasible, and acceptable interventions to reduce the environmental impact of operating theatres.

## Methods

Methodologies were combined to harmonize knowledge gaps and co-prioritize interventions that are feasible and acceptable to stakeholders<sup>11</sup>. This global co-prioritization exercise consisted of four phases:

- Phase 1: a systematic review and global consultation with perioperative healthcare professionals (HCPs) to longlist candidate interventions with evidence of effectiveness.

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- Phase 2: iterative thematic analysis to shortlist these interventions.
- Phase 3: co-prioritization of these shortlisted interventions by key stakeholders, including clinicians and patients, based on feasibility, acceptability, and safety.
- Phase 4: ranking of these interventions into an ordered list of actionable interventions across both high-income countries (HICs) and low-middle-income countries (LMICs).

### Phase 1: systematic review and global consultation survey

A systematic review of the literature was performed according to the PRISMA guidelines to identify studies describing interventions to reduce the environmental impact of operating theatres<sup>12</sup>. As a pragmatic approach in this study, reduced environmental impact was defined as reduction of carbon output (measured with a carbon dioxide equivalent (CO<sub>2</sub>e) calculation) or reduction of plastic waste. A search was performed using MEDLINE, Embase, and Cochrane Library databases, searching for studies published until 3 December 2021. A summary of search terms used for the systematic review are presented in [Table S1](#). Both peer-reviewed full papers and other article types (for example conference abstracts and reports) were eligible. Exclusion criteria were: interventions delivered outside of the operating theatre; and (ii) non-surgical patients (that is endoscopy). Full texts of potentially eligible trials were obtained and independently evaluated for inclusion in the review based on the inclusion criteria. Studies describing surgery for any condition and anaesthesia of any modality were included. References of all included studies were reviewed to ensure relevant studies were included. All studies were independently assessed by two reviewers (Sivesh Kamarajah and Harvinder Mann). When there was disagreement, the senior authors (Aneel Bhangu, James Glasbey, Dmitri Nepogodiev, or Elizabeth Li) assessed the study to reach a consensus. The extracted list of interventions was combined to form the basis of the longlist.

Next, a global consultation survey was conducted with perioperative HCPs (such as surgeons, anaesthetists, theatre practitioners, nurses, and hospital managers) sampled from across the National Institute for Health and Care Research (NIHR) Global Health Unit on Global Surgery network. The consultation survey aimed to explore the current adoption of interventions identified in the systematic review, collate novel, unpublished interventions with early evidence of effectiveness, and identify any barriers to implementing these interventions. The final longlist of interventions were classified into the following categories, as previously described: scope 1: direct emissions; scope 2, emissions from electricity; or scope 3, all other indirect emissions from the supply chain<sup>13</sup>.

### Phase 2: shortlisting of interventions

Individual interventions (transcribed verbatim) underwent three-stage thematic content analysis, consisting of coding, assigning descriptive themes, and then generating summarized interventions across each of the three scopes. Each intervention was double-coded, with analysis performed iteratively by four researchers (Sivesh Kamarajah, James Glasbey, Dmitri Nepogodiev, and Aneel Bhangu) to a point of saturation. As interventions frequently targeted the same carbon-reduction activities, these were combined to reduce redundancy and/or duplication. Differences between specific components of the intervention (for example action, actor, context, target, and

time) were recorded<sup>14</sup>. Consensus on phrasing for the combined intervention domains were agreed across the research team. The results of the thematic analysis were reviewed across two focus-group discussions, including international representation across the perioperative clinical and management teams.

### Phase 3: co-prioritization with clinicians and patients

After shortlisting, a second global consultation was conducted with perioperative HCPs and hospital managers, to explore perceptions of acceptability, feasibility, and safety of candidate interventions from phase 2. In parallel, a Patient Advisory Group (PAG) was established in partnership with Patients and Research Together (PaRT) from Bowel Research UK in line with NIHR Centre for Engagement and Dissemination (CED) recommendations<sup>15</sup>. Diverse representation was proactively sought in accordance with the INCLUDE principles in inclusive research design<sup>16</sup>. The PAG co-developed a patient and public-facing survey using lay language that was disseminated across a broad network of charities and patient groups. The survey targeted those who had had or were currently awaiting surgery. The results of the clinician survey were reviewed by the PAG in an advisory group meeting to further develop emerging themes and inform phase 4 ranking. Members of the PAG were included as equal co-authors in this study's collaborative author group.

### Phase 4: ranking of interventions based on feedback from the Patient Advisory Group, the results of phase 3

Co-prioritization informed ranked lists of interventions based on HCPs' perceptions of feasibility; patient and public co-authors highlighted that patients would be largely unaware of many changes to greener practices in operating theatres, but that they perceived sustainable care to be a marker of a high-quality health system and so ease of implementation was a priority. The ranked lists are presented stratified by country-income group (HIC versus LMIC) of respondents according to World Bank 2019 definitions<sup>17</sup>.

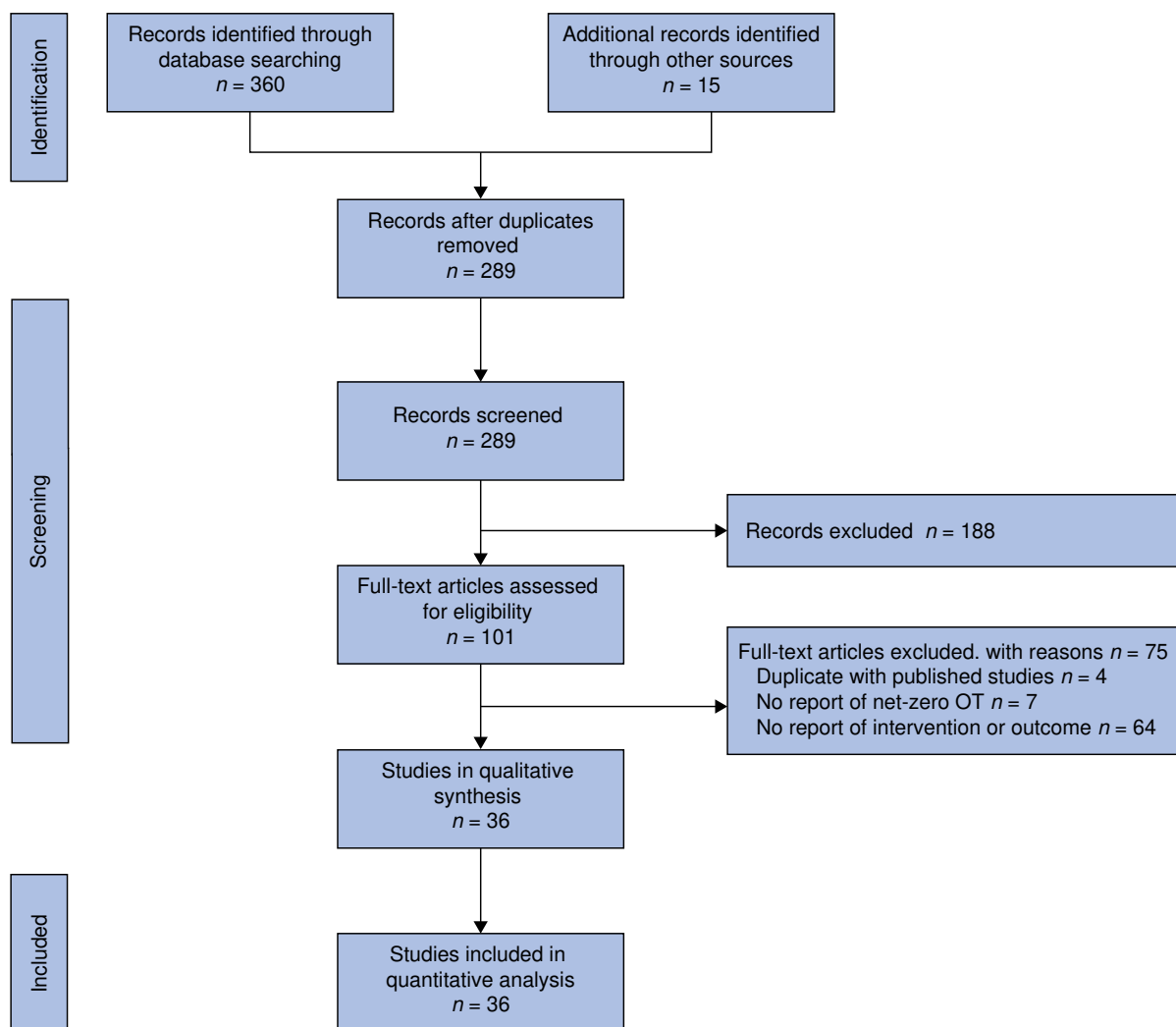
### Ethics

Ethical approval was not required as the global consultation survey gathered fully anonymized expert opinions from our network of research collaborators and co-authors. INVOLVE guidance states ethical approval is not needed for research activities involving patients and the public when they have active involvement, providing opinions and specialist knowledge or advice<sup>18</sup>.

## Results

### Phase 1: systematic review and global consultation survey

The systematic review identified 289 studies, of which 36 ([Table S2](#)) were included after full-text review ([Fig. 1](#)). These reported 43 interventions to reduce the environmental impact of operating theatres. To minimize redundancy, comparable interventions were combined after consensus agreement across the research team ([Table S3](#)). [Table 1](#) shows the 24 agreed interventions generated during this process. The majority of interventions (29/36) were from single-centre studies with no evidence of scaling across multiple departments or hospital networks ([Table S2](#)). None of the studies reported safety implications of these interventions (0/36).



**Fig. 1** PRISMA flow chart of studies included in the systematic review of interventions to reduce the carbon footprint of operating theatres (OT).<sup>19</sup>

A total of 3042 professionals from 117 countries participated in the global consultation (Table S4), of which 36.0 per cent of respondents were from LMICs. Environmental-impact reduction interventions reported in the literature were often not in current practice (median of 24.5 (interquartile range 21.8–35.8) per cent; Table 1). The consultation identified a further 88 unpublished interventions from participants (Table S5). As part of this consultation, HCPs were also asked their opinions on sustainable surgical practices. Of the perioperative professionals, 96.5 per cent were willing to change practice, but only 2.3 per cent felt that there were no barriers to implementation of environmentally beneficial surgical practices in their hospital (Table 2 and Table S6). When exploring barriers to greener operating theatres, there were low rates of sustainable practice plans (17.0 versus 14.4 per cent in LMICs and HICs respectively) and operating theatre sustainability leads (14.1 versus 10.0 per cent), and a lack of information about which green surgery initiatives should be prioritized (78.2 versus 76.0 per cent in LMICs and HICs respectively).

### Phase 2: shortlisting of interventions

During thematic analysis, the longlist was reduced from 112 interventions (24 from the systematic review and 88 from the global consultation) to 15 intervention domains (Fig. 2).

### Phase 3: co-prioritization with clinicians and patients

Co-prioritization was conducted with 5218 perioperative HCPs and hospital managers from 132 countries, of which 2295 of respondents (44.0 per cent) were from LMICs (Table S4). Perioperative professionals considered most of the shortlisted interventions to be safe and feasible, although safety concerns for interventions were generally higher in LMICs (median of 15.8 (range 8.9–40.1) per cent) than HICs (median of 9.1 (range 4.2–29.9) per cent) (Table 3 and Table 4). Interventions raising highest concerns were re-sterilization of ‘single-use’ consumables (40.1 versus 29.9 per cent in LMICs and HICs respectively) and reduction of gases for minimally invasive surgery (21.5 versus 26.0 per cent in LMICs and HICs respectively). Despite being ranked third highest for safety concerns by professionals in LMICs (23.1 per cent; Table 3), introducing surgical devices that can be reused was identified as the most feasible (74.3 per cent). Free-text feedback from LMIC professionals and the international steering group indicated that this was due to pre-existing wide reuse of surgical devices due to financial and resource constraints.

Patient co-prioritization was conducted with 75 patients from the UK only. In general, patient acceptability for patient-facing



**Table 1 Current global practice regarding environmental-impact reduction in operating theatres, organized by scope of the greenhouse gas protocol<sup>13</sup>**

	Overall	HIC	LMIC
<b>Scope 1</b>			
Reducing desflurane use	25.3	31.1	18.6
Removing desflurane from theatre	18.8	19.7	17.9
Reducing nitrous oxide use	32.4	33.4	31.3
Removing nitrous oxide from theatre	23.6	20.8	26.3
Using low flow when using volatile anaesthetics	39.4	40.5	38.2
Mandating total intravenous anaesthesia	13.9	12.1	16.0
<b>Scope 2</b>			
Turning off lights in theatre at night/weekends	61.1	60.6	61.9
Motion-activated lights	14.8	14.3	15.7
Turning down heating/air conditioning at night/weekends	40.5	31.5	52.0
Installing light-emitting diode (LED) lights	31.5	26.1	38.6
Switching off taps between hand washing	64.1	62.4	66.7
<b>Scope 3</b>			
Recycling non-contaminated waste	34.0	38.0	27.5
Reducing plastic syringe use	13.2	12.7	13.9
Reducing unnecessary intravenous fluid use	35.4	30.7	42.1
Reducing unnecessary intravenous drug use	37.3	32.0	44.5
Using reusable surgical gowns	23.3	14.8	36.9
Using reusable surgical drapes	23.1	14.2	37.5
Reducing single-use instruments	23.1	15.7	34.6
Switching blue sterile tray wraps to metal canister trays	23.4	18.4	31.6
Redesigning trays for efficiency	19.4	16.4	24.0
Reducing disposable glove use for simple patient transfers	16.5	11.0	24.9
Using reusable laparoscopy ports	26.8	13.7	45.2
Reserving laparoscopic and robotic surgery	37.0	33.6	42.1
Using reduced packaging	22.7	17.0	30.2

Values are percentages. Scope 1, direct emissions; scope 2, emissions from electricity; and scope 3, all other indirect emissions from the supply chain.<sup>13</sup> HIC, high-income country; LMIC, low-middle-income country.

**Table 2 Barriers to implementing green surgery initiatives identified by perioperative professionals**

	Overall	HIC	LMIC
Lack of information about which green surgery initiatives should be prioritized	77.0	76.0	78.2
Lack of guidance for how to implement green surgery initiatives	75.2	74.0	67.6
Lack of support from hospital management for green surgery initiatives	59.0	60.2	57.5
Lack of engagement by theatre team with green surgery issues	48.4	46.8	50.5
Lack of hospital sustainability lead	76.2	75.5	77.2
Lack of operating theatre sustainability lead	88.4	90.0	95.9
Perceived cost of implementing green surgery initiatives	62.3	60.9	64.1
Lack of time to implement green surgery initiatives	37.6	44.7	28.7
None of the above is a barrier at my hospital	2.3	2.4	2.2

Values are percentages. HIC, high-income country; LMIC, low-middle-income country.

intervention domains was high (median of 93 (interquartile range 90–96) per cent). The only interventions with patient acceptability less than 90 per cent were using local rather than general anaesthetic (84 per cent) and reuse of single-use consumables (86 per cent).

Patients also highlighted the need for an environmentally friendly operation (97 per cent agreed) if interventions were safe and effective, and 95 per cent felt this was important to their community (Table S7). In terms of the financial implications of implementing these interventions, patients were divided, with 51 per cent supportive of carbon reduction even if it meant higher costs to the health service. Respondents agreed that health services should promote their efforts to reduce the carbon footprint in surgery (75 per cent) and, to a lesser extent, that patients should be empowered to make choices to reduce the carbon footprint of their operation as part of the consent process (70 per cent; Table S7). The PAG enriched this by adding that with concerns around the time of surgery for their own recovery and safety, these factors would take precedent over making more carbon-conscious choices during surgery.

#### Phase 4: ranking of final interventions

The final intervention domains were ranked based on feasibility (Fig. 2), as determined by perioperative professionals from LMICs (Table 3) and HICs (Table 4), with clinician acceptability, safety, and patient acceptability displayed alongside each (Table 5). The top three ranked interventions from LMICs were: introducing reusable surgical devices; reducing use of consumables; and reducing the use of general anaesthesia. The top three ranked interventions from HICs were: introducing recycling; reducing use of anaesthetic gases; and appropriate clinical waste processing.

#### Discussion

This study has identified and ranked a list of interventions that are feasible and immediately actionable for frontline teams and managers to implement within their hospitals. This provides teams around the world a place to start their journey to decarbonizing operating theatres and highlights clear interventions to take forward into future research. This list was divided into two, relevant to both HIC and LMIC settings, to broadly reflect differences in healthcare resourcing. The safety concerns of respondents indicated that further evaluation of some interventions is needed to reassure surgical teams and patients. These were largely around surgical site infections and reusable equipment, and chest infections with changes in anaesthetic practices. Evaluation through well designed, efficient-implementation research is needed to test whether safe and effective measures can be scaled at national and international levels.

Methodologies were combined in this study to try to overcome some of the problems that have limited wide-scale uptake of carbon reduction in operating theatres to date. First, the systematic review identified numerous single-centre studies and opinion pieces, indicating only the very early phases of evidence available. It is very hard for frontline teams to know what to do, and where to start, when reducing their environmental impact. Recent initiatives, such as the UK's Intercollegiate Green Theatre Checklist, are complementary, but contain too many recommendations for immediate implementation (16), and neglect differences in health resourcing, beliefs, and team structures around the world<sup>20</sup>. Second, sustainably reducing carbon in operating theatres is not simple, as teams rotate regularly, and team behaviour needs to be supported by organizational-level change<sup>21</sup>. The systematic review adds to the current literature by identifying barriers and solutions to creating change. This includes a lack of leadership for carbon-reduction initiatives specific to the operating theatre, and a lack of guidance as to which initiatives to prioritize; this is now provided by this manuscript.

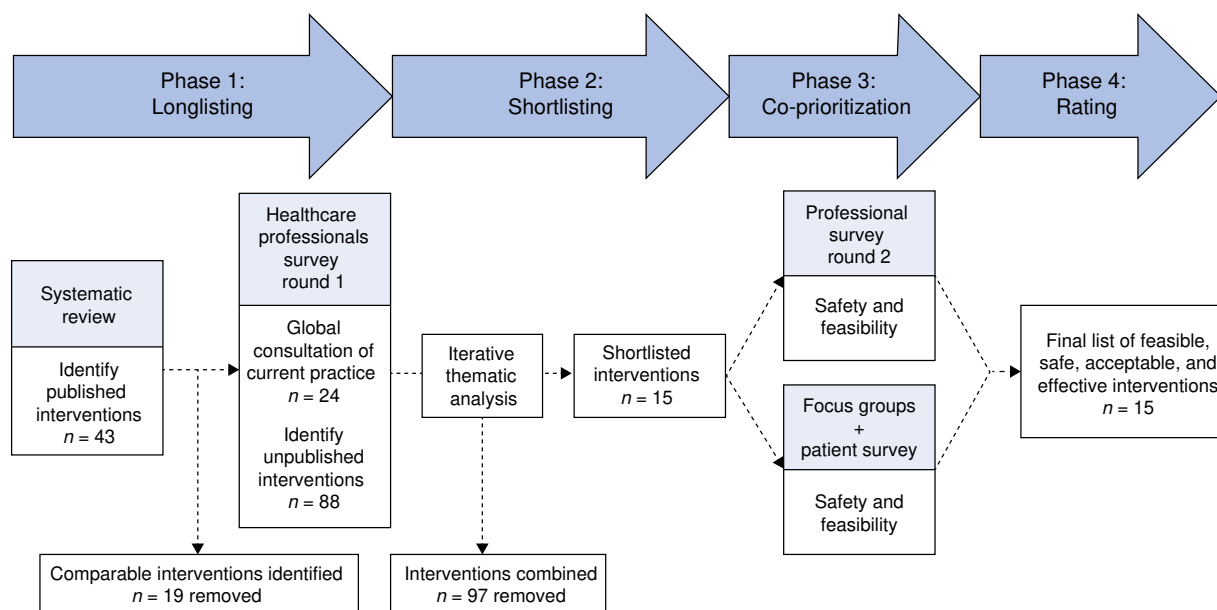


Fig. 2 Co-prioritization of interventions to reduce the carbon and environmental impact of operating theatres

Table 3 Comparison of perioperative professionals' prioritization voting in low–middle-income countries, ranked by clinicians' perceived feasibility

	Feasibility	Safety concerns	Unintended consequences
Introduce surgical devices that can be reused*	74.3	23.1	23.0
Reduce consumables used*	72.5	16.0	16.9
Reduced general anaesthesia used, increased local/regional anaesthesia†	72.3	8.9	13.4
Reduce energy and water use‡	68.1	15.8	19.4
Increase use of consumables that can be easily recycled*	67.5	14.2	17.5
Ensure appropriate use of clinical waste‡	66.9	12.1	15.2
Introduce reusable surgical gowns and drapes‡	66.8	29.8	29.7
Reduce impact of personal protective equipment (PPE)‡	66.0	22.3	23.8
Reduce the use and wastage of anaesthetic gases‡	65.8	19.4	18.3
Streamline theatre processes‡	64.9	11.0	13.4
Make more use of lightly packaged consumables*	63.0	14.2	16.9
Introduce recycling‡	60.8	13.6	15.5
Introduce re-sterilization and reuse of single-use consumables*	58.0	40.1	39.0
Reduce the impact of surgical fumes§	55.2	12.3	14.4
Reduce the use of gases for minimally invasive surgery¶	48.4	21.5	19.6

Values are percentages. \*Responses from surgeons, theatre nurses, Operating Department Practitioners, and theatre managers/stores only. †Responses from anaesthetists and anaesthetic nurses only. ‡Responses from all participants. §Responses from surgeons and theatre nurses only. ¶Responses from surgeons only.

The strengths of this study include the large network of respondents, from diverse international settings, improving the generalizability of the results. Second, this body of work combines patient and theatre professional views on the interventions to be used in theatre, consulting with a wide range of stakeholders. Public engagement and patient perspectives are essential, given that the benefits of carbon- and waste-reducing interventions are likely to be mainly for the whole community rather than the patient being treated alone<sup>22</sup>. The use of complementary methodologies took the best available evidence, which was found to be widely heterogeneous, and converted it into practical measures suitable for large-scale adoption. This is important, as the next step to create change is to evaluate implementation and scaling across countries and not rely on single-centre enthusiasts.

This study also has limitations, which mainly reflect the very early nature of the literature. The network's judgements on feasibility are relatively subjective and not necessarily borne

through lived experiences (for example installing solar panels for hospital energy). Some interventions that were judged feasible might also require additional, hidden infrastructure changes (for example recycling). This is similar for effectiveness, which reflects an early evidence base and is the best knowledge available until further research emerges. As a result, there was no differentiation between carbon and plastic waste reduction in the ranked co-prioritization lists, and effectiveness estimates were not listed in these tables. Although theatre professionals from LMICs made up 44 per cent of all professionals and managers participating, representation of patients from LMICs was missing from our patient network and is needed in future studies.

This study can be used to point to specific, tangible, next-step research. Where safety concerns were raised, randomized trials with safety outcomes are required, for example evaluating reusable drapes, changes in use of harmful anaesthetic gases, and increase in local anaesthetic repair of inguinal hernia<sup>23</sup>.

**Table 4 Comparison of perioperative professionals' prioritization voting in high-income countries, ranked by clinicians' perceived feasibility**

	Feasibility	Safety concerns	Unintended consequences
Introduce recycling*	76.0	4.2	6.7
Reduce the use and wastage of anaesthetic gases§	71.9	10.1	12.2
Ensure appropriate use of clinical waste*	69.7	4.2	6.0
Reduce consumables used†	68.7	9.1	11.1
Reduce energy and water use*	68.3	8.9	9.9
Reduce the impact of surgical fumes‡	68.2	6.2	8.8
Make more use of lightly packaged consumables†	64.3	6.0	7.8
Increase use of consumables that can be easily recycled‡	60.7	7.5	9.2
Streamline theatre processes*	57.2	6.8	7.8
Reduced general anaesthesia used, increased local/regional anaesthesia§	55.2	10.1	14.9
Introduce surgical devices that can be reused‡	53.2	12.6	14.0
Reduce impact of personal protective equipment (PPE)*	53.0	11.7	13.4
Introduce reusable surgical gowns and drapes*	46.2	16.4	18.9
Introduce re-sterilization and reuse of single-use consumables‡	33.6	29.9	28.4
Reduce the use of gases for minimally invasive surgery¶	32.2	26.0	22.4

Values are percentages. \*Responses from all participants. †Responses from surgeons, theatre nurses, Operating Department Practitioners, and theatre managers/stores only. ‡Responses from surgeons and theatre nurses only. §Responses from anaesthetists and anaesthetic nurses only. ¶Responses from surgeons only.

**Table 5 Summary of patient and clinician voting during co-prioritization at the end of phase 4, ranked by feasibility overall (low-middle-income countries and high-income countries)**

Stakeholder	Clinicians			Patients	
	Prioritized interventions	Feasibility	Safety	Lay language summary	Acceptability*
Shortlisted intervention		Safety concerns	Unintended consequences		
Reduce consumables used‡	70.4	12.1	13.7	Using less disposable ('throwaway') equipment, for example by only opening items when needed rather than 'just in case'	95
Introduce recycling‡	69.3	8.3	10.6	Increasing recycling of the paper, plastics, and metals used in theatre	96
Reduce the use and wastage of anaesthetic gases§	69.2	14.2	14.9	Using strategies to reduce the use of greenhouse gases by the anaesthetist when you are put to sleep for your operation (Not patient facing)	91
Ensure appropriate processing of clinical waste‡	68.5	7.7	10.0		–
Reduce energy and water use‡	68.2	11.9	14.1	Reducing heating, lighting, and water usage in empty operating theatres (Not patient facing)	99
Make more use of lightly packaged consumables†	63.7	9.6	11.8		–
Increase use of consumables that can be easily recycled‡	63.7	10.4	12.9	(Not patient facing)	–
Reduced general anaesthesia used, increased local/regional anaesthesia§	62.7	9.6	14.2	Where possible, using local anaesthetic rather than general anaesthetic for an operation	84
Reduce the impact of surgical fumes¶	62.5	8.9	11.3	Capturing and safely removing any fumes created during surgery	97
Introduce surgical devices that can be reused‡	62.5	17.2	18.0	Choosing surgical equipment that can be sterilized and safely reused in more than one operation (Not patient facing)	95
Streamline theatre processes‡	60.6	8.6	10.3		–
Reduce impact of personal protective equipment (PPE)‡	58.7	16.4	18.0	(Not patient facing)	–
Introduce reusable surgical gowns and drapes‡	55.3	22.3	23.7	Using personal protective equipment that can be washed and sterilized to safely reuse across multiple operations	92
Introduce re-sterilization and reuse of single-use consumables‡	44.3	34.4	33.1	Sterilizing and safely reusing equipment that is marketed as 'single-use' by manufacturers	86
Reduce the use of gases for minimally invasive surgery#	39.3	24.0	21.2	Safely reducing the use of greenhouse gases during keyhole surgery	92

Values are percentages. \*Proportion of patients reporting 'very comfortable', 'comfortable', or 'neutral' about the acceptability of this intervention. †Responses from surgeons, theatre nurses, Operating Department Practitioners, and theatre managers/stores only. ‡Responses from all participants. §Responses from anaesthetists and anaesthetic nurses only. ¶Responses from surgeons and theatre nurses only. #Responses from surgeons only. –, not applicable.

Where measures are likely to be both safe and effective, quality-improvement approaches can help to scale changes in energy supply and use, changes in recycling, and changes to

instrument use, and identify the best models to scale this learning around the world. Qualitative methods will be required to create data-driven approaches to behaviour change and engaging senior

management (complex intervention research), the role of leaderships, and the best way to train and sustain diverse teams in carbon reduction<sup>24-26</sup>.

## Collaborators

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## Supplementary material

Supplementary material is available at *BJS* online.

## Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material.

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