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Optimising Surgical Instrument Trays for Sustainability and Patient Safety by Combining Actual Instrument Usage and Expert Recommendations

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Abstract: Annually, over 300 million surgeries occur globally, requiring numerous surgical instruments. However, many instruments on the tray are returned to the central sterile supply department (CSSD) unused, creating an unsustainable pattern of unnecessary consumption. To address this, we developed a method for optimising surgical instrument trays (SITs) that is straightforward to implement in other hospitals. This optimisation aims to enhance patient safety and sustainability and to improve working conditions and reduce costs. We identified actual instrument usage (IU) in the operating room (OR) and obtained expert recommendations (ERs). Data from both methods were combined in a computer model (CM) to adjust the SITs. The performance of the adjusted SITs was assessed over a year. IU of three different SITs was collected during 16 procedures (mean = 28.4%, SD = 6.4%). Combining IU and ERs resulted in a 36.7% reduction in instruments and a 31.3% weight reduction. These measures contribute to reducing the carbon footprint and enhancing sustainability. During the evaluation of the new SIT contents (n = 7 procedures), mean IU increased from 28.4% (SD = 6.4%) to 46.5% (SD = 11.0%), with no missing instruments during surgery. A one-year follow-up showed no need for further alterations. Combining both methods yields better results than using them individually, efficiently reducing unnecessary items in SITs without compromising patient safety.

Keywords: surgical instrument tray optimisation; sustainability; OR efficiency; computer model; instrument reduction; resource use; patient safety

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1. Introduction

Annually, over 300 million surgeries are performed worldwide [1], necessitating the use of numerous surgical instruments that are reprocessed in the central sterile supply department (CSSD). In hospitals, the CSSD is a resource-intensive area where a significant amount of water, chemicals, and energy are used. Following surgery, at the CSSD, all instruments undergo a process involving cleaning, disinfection, manual inspection, and sterilisation after each procedure to ensure patient safety, regardless of their actual utilisation during a surgical procedure. Research indicates that the usage of surgical instruments ranges between only 13.0% and 21.9% of the total across different surgical instrument trays (SITs) [2,3]. Consequently, the majority of the instruments are returned to the CSSD unused, leading to unnecessary resource use.

Minimising the inclusion of unnecessary instruments on SITs will enhance patient safety by improving the tray's clarity, thereby reducing the chances of errors in counting the instruments. Additionally, it will diminish environmental impact and contribute to cost savings [3,4]. Benefits such as reduced tray weight and decreased processing and preparation times are followed by increased personnel satisfaction [3,5–7]. Thus, optimising the contents of SITs will yield multiple advantages without compromising quality of care [8,9].

Previously, the reduction and optimisation of SITs were solely based on a data-driven or expert-driven approach, for example, only on calculated utilisation rates, group reviews, or group consensus models [9–12]. While this approach integrates valuable clinical perspectives, it is time-consuming, highly subjective, and often conducted in small settings, making it challenging to scale up. More recent studies have shown mathematical optimisation models or combinations of methods to improve SIT optimisation, for example, by combining both (historical) usage rates and mathematical modelling [13,14] or the combination of a clinician review, usage rates, and a cost-based inflection point model [15]. However, most studies that employ mathematical optimisation models rely on simulated data.

For an extensive overview of studies on this topic, readers are encouraged to consult the literature reviews by Ahmadi et al. [16] and Dos Santos et al. [17]. However, these studies do not observe the performance of the optimised SIT, or they do so only over a brief period. This lack of long-term evaluation represents a significant gap in the current research. Our study addresses this by developing a self-learning model for SIT optimisation designed for straightforward implementation in other hospitals and by rigorously assessing the performance of the optimised SITs over an extended period.

We hypothesise that integrating actual instrument usage (IU) rates with expert recommendations (ERs) into a self-learning computer model (CM) would result in an effective and patient-safe reduction compared to using either approach alone. Additionally, we introduce a method for calculating an appropriate cut-off percentage in a data-driven approach, which has not been extensively covered in other research. Lastly, by assessing the performance of the newly optimised SITs over a one-year period, we aim to determine whether the changes lead to lasting improvements.

2. Methods

This observational study was conducted at the gynaecology department of the Leiden University Medical Centre (LUMC) in the Netherlands, where over 700 gynaecological surgeries are performed annually. Approval of the Institutional Review Board (IRB) was not required for this study, as it did not meet the criteria according to the Medical Research Human Subjects Act.

It spanned a 7-month period during which gynaecological oncological laparotomies, such as total hysterectomies, adnexal excisions, and debulking procedures, were observed. These specific procedures were chosen because they involve the use of three separate SITs per procedure, enabling to observe multiple trays, assess instrument variations, and train the CM. However, the described approach is applicable to all types of SITs across various surgical specialties. The chosen procedures necessitated a basic tray (BT), a gynaecological tray (GT), and an oncological tray (OT), which we aimed to optimise by incorporating (1) actual IU in the operating room (OR) and (2) ERs. Through the integration of these approaches, our goal was to achieve a secure and user-friendly methodology.

The developed methodology for SIT optimisation consists of five steps:

1. Measuring actual IU during the surgical procedures.
2. Collecting ERs.
3. Creating a self-learning CM for SIT optimisation.
4. Combining two approaches (IU and ERs) in the CM and approval of final SIT content.
5. Evaluating adjusted SITs in the OR.

2.1. Measuring Actual IU during the Surgical Procedures

Three gynaecologists were observed. They performed a total of 96 oncological laparotomies (requiring the use of BT, GT, and OT) in the year prior to this study. First, actual IU was determined by counting instrument use manually in the OR by a trained author. A total of 16 randomly selected surgeries for gynaecological oncology were observed, requiring BT, GT, and OT, which consisted of 62, 43, and 50 instruments, respectively, totalling 155 instruments. Total IU was counted according to the methodology in Figure 1. Used instruments were marked '1', missing data points '−1', and unused instruments '0'. The data were organised in Microsoft® Excel® (Version 2308 Build 16.0.16731.20542) and imported in MATLAB (MATLAB, version R2022b) for processing. For data information, see Supplementary Materials.

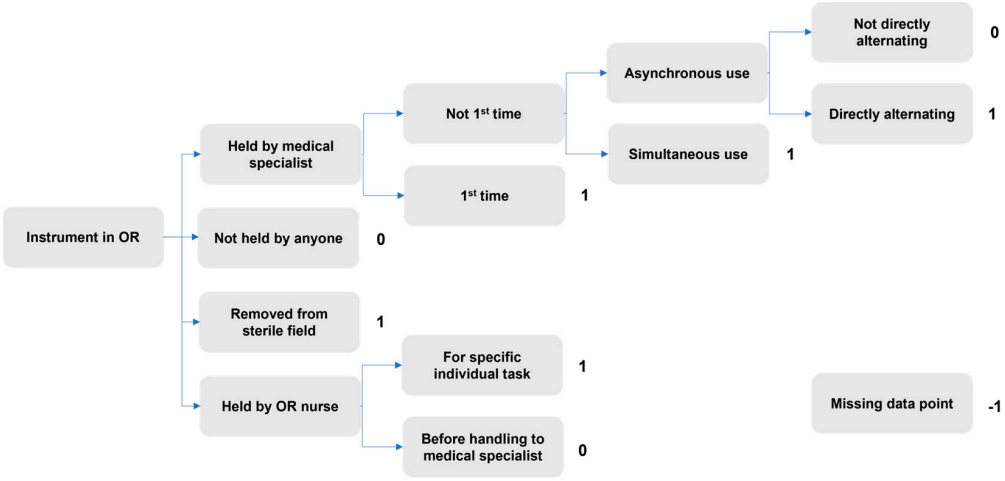

Figure 1. Decision tree for data collection of the actual IU. Used instruments were marked '1', missing data points '−1', and unused instruments '0'. IU: instrument usage.

2.2. Collecting ERs

Initially, subjective IU and tray composition preferences were determined through a group session involving the three observed gynaecologists. They were tasked with estimating the frequency of IU on a scale of 0–3 (where 0 is never, 1 is sometimes, 2 is often, and 3 is always) and suggesting the minimum and necessary quantities of each specific instrument for all three SITs. The responses were recorded in Excel and subsequently uploaded into the CM. The group session allowed for discussion but required a unanimous decision in the end.

Secondly, the three gynaecologists were tasked with assessing the combined risk to patient safety associated with each available instrument in the event of its unavailability during the procedure. They developed and utilised a scale from A to D, where A was no risk to patient safety, B was an acceptable risk (without permanent damage to the patient), C was an unacceptable risk (with permanent damage to the patient), and D was a critical, life-threatening risk. Furthermore, they determined which instruments, based on the scale, were classified as low risk (A or B) or as high risk (C or D). If an instrument fell into the high-risk category, it was excluded from automatic removal. Although the group session allowed for discussion, a unanimous verdict was deemed necessary to include the instruments in a certain group (A–D). For further insights into the decisions made in the ER assessment, please refer to Supplementary Materials.

2.3. Creating a Self-Learning CM for SIT Optimisation

The CM, automatically proposing a new SIT composition, was designed in MATLAB. Detailed step-by-step instructions and scripts can be found in the Supplementary Materials for replication. Initially, the first model ("Boxplots.m") computed IU percentages for all instruments related to the SITs. The newly proposed SIT composition was, however,

formulated based on two key variables: the minimal IU percentage, further referred to as the cut-off point, which determined whether an instrument should be on the tray; and another variable established by the ERs that indicated if the instrument was high risk (C or D) and could not be omitted. Concerning the first variable, for instance, when a cut-off point of 5% was selected, all instruments that were used in at least 5% of the procedures in the dataset were retained on the SIT. If two identical instruments were present on the SIT and only one surpassed the designated IU threshold, only that particular instrument was suggested for inclusion in the new tray composition. As for the second variable, instruments deemed high risk (C or D) were exempted from automatic removal. Therefore, the second and third models were used ("Reduction_highrisk.m" and "Reduction_lowrisk.m"). These two iterating reduction models determine the recommended new number of instruments for every cut-off point. The fourth and final model ("Comparison.m") compares the SIT recommendations based on different cut-off points to the suggested tray compositions based on the ERs. It also compares the suggestions of the gynaecologists, and finally, it performs an analysis to determine the possibility of missing an instrument during surgery.

2.4. Combining Two Approaches (IU and ERs) in the CM and Approval of Final SIT Content

The final MATLAB model processed the combined data (IU and ERs) and suggested a new SIT composition. A cut-off point of 10% minimal usage was used. The model's output was utilised to challenge the gynaecologists' recommendations, enabling the potential removal of more instruments from the SITs. However, to ensure acceptance of the new tray contents and to address any concerns about patient safety, the gynaecologists and OR nurses had the final authority to approve any changes to the SITs. Consequently, the model's output was revisited and discussed once again with the gynaecologists and OR nurses before usage in the OR. The step to include OR nurses in the final approval was crucial because OR nurses work according to a specific methodology. Their requirements, such as maintaining even numbers of most instruments for easier counting and including extra items to assist with tasks beyond the surgical procedure, were considered to ensure acceptance of the new contents. Adjustments were made based on the feedback from both the gynaecologists and OR nurses, ensuring that the final SIT composition met the necessary standards.

2.5. Evaluating Adjusted SITs in the OR

The SITs, featuring a new composition, were introduced in the OR for evaluation. The reduced contents were organised within the 'new' SIT. To ensure all instruments remained available for urgent needs during the evaluation phase, the removed instruments were placed on a separate SIT available during the surgeries in this phase. This approach aimed to minimise the likelihood of missing an instrument during surgical procedures.

The trained author (T.v.T.) supervised multiple surgeries to assess the new SIT composition. Individual IU was recorded again, and these data were utilised to evaluate the performance of the new tray composition alongside the theoretical performance of alternative SIT compositions. The count of theoretically missed instruments during the evaluation phase was used to assess potential risks associated with different SIT optimisation methods.

Finally, over the subsequent year after introducing the new SITs, observations on adjustments to the new SITs were made to determine whether further alterations were necessary.

3. Results

3.1. Instrument Usage in the OR

In total, 23 gynaecological oncological laparotomies were observed in the OR by the trained author, with a total duration of 4557 min. All procedures were performed by one of the gynaecologists from the same group of three gynaecologists. Of these surgeries, 16 were used to analyse the methodology and devise a new SIT composition. The other seven surgeries were used to evaluate the adjusted SITs in the OR, as discussed below. The

mean IU for the first 16 procedures was 28.4% (SD = 6.4%) across the three SITs used for gynaecological oncological laparotomies.

3.2. Determining the Cut-Off Point

To establish the methodology of using both subjective and objective data, IU and ER data were combined in the CM. Figure 2 shows the model output—the suggested number of instrument removals—for all cut-off points across the SITs used. The overall discrepancy between subjective (ERs) and objective (actual IU) recommendations served as a performance index to ascertain the optimal cut-off point for minimal IU percentages.

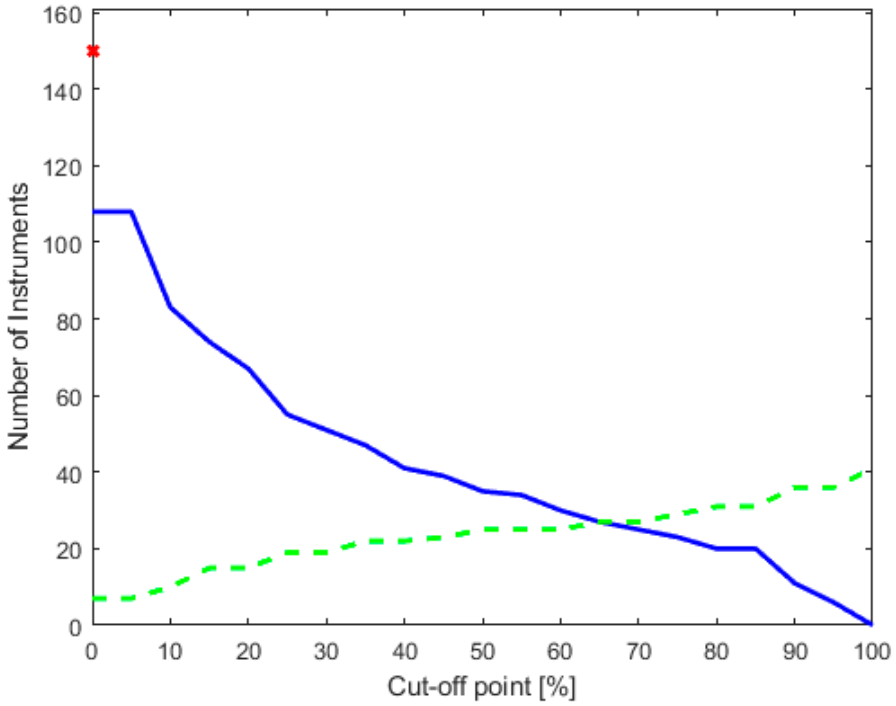

Figure 2. Instrument reduction after combining actual IU and ERs by CM. The *X*-axis shows the cut-off point (minimal usage percentage of instruments), whereas the *Y*-axis shows the number of recommended instruments to stay on the SIT. The red 'X' marks the initial number of instruments before any reduction methods were applied. The solid blue line shows the suggested instrument removals. The dashed green line visualises the suggested number of high-risk instrument removals.

Upon analysis, the authors concluded that the preferred cut-off point, aiming for minimal variability between the data and the gynaecologists' recommendations, was 10%. With this cut-off point, the ERs suggested the removal of 39% of surgical instruments, and the data suggested the removal of 38% of all instruments (Table 1). We observe that there is no substantial difference between the individual methods when using the 10% cut-off point, and at higher cut-off points, the reduction potential based on IU increases. Despite this, we opted for the 10% cut-off point due to the observed discrepancy between the two methods. It became apparent that with this 10% cut-off, 19% of the instruments are recommended on the tray based solely on IU data (10%) or solely by ERs (9%). Even though both methods achieved similar reduction percentages, they disagreed on 19% of the complete instrument set. For other cut-off points, the differences between IU data and ERs were more pronounced, and for this reason, a cut-off point of 10% was chosen.

Table 1. Cut-off points and related recommendations by the CM considering ER and IU data.

Cut-Off Point	Only Recommended on Tray by ERs	Only Recommended on Tray by IU	New Number of Instruments Solely Based on ERs	New Number of Instruments Solely Based on IU	Total Difference between ERs and IU
0%	2%	18%	91 (−39.3%)	115 (−23.3%)	20%
5%	2%	18%	91 (−39.3%)	115 (−23.3%)	20%
10%	9%	10%	91 (−39.3%)	93 (−38.0%)	19%
15%	11%	9%	91 (−39.3%)	89 (−40.7%)	20%
20%	15%	9%	91 (−39.3%)	82 (−45.3%)	24%
25%	20%	9%	91 (−39.3%)	74 (−50.7%)	29%

Legend: CM: computer model; ERs: expert recommendations; IU: instrument usage.

3.3. Instrument Misses on SITs

Although the reduction potential is not substantially different between IU and the ERs, the distinct reduction methods result in different theoretical instrument 'misses' during procedures with the CM (Table 2). A reduction based on IU with a cut-off point of 10% or a reduction based solely on ERs causes a 'miss' of 3.9% or 8.7% of the instruments, respectively. A tray composition solely based on the gynaecologists' recommendations would thus have resulted in 27 instrument misses (8.7%), among which 2 instruments were high-risk items. However, a tray composition based on the objective data for a 0% cut-off point would have caused a single low-risk miss (0.3%). The new methodology combining both the IU and ER methods maximises the removal of instruments (55 in this instance) without causing any instrument misses, as it allows for the exclusion of high-risk items through the use of ERs to ensure patient safety. This combined approach thus leads to a more substantial, effective, and safer reduction compared to using only one of the methods.

Table 2. Theoretical instrument misses during evaluation. Theoretical predictions of instrument misses during a surgical procedure, as predicted by the CM based on the selected reduction method (IU with a specified cut-off point or ERs). For the risk of missing an instrument during a surgical procedure, a scale from A to D was used, where A was no risk to patient safety, B was an acceptable risk (without permanent damage to the patient), C was an unacceptable risk (with permanent damage to the patient), and D was a critical, life-threatening risk. Both A and B are considered 'low risk', while C and D are considered 'high risk'. The 'new methodology' is the combination of a cut-off point of 10% of IU and the ERs in the CM.

Reduction Method	Suggested Item Removals	Low- and High-Risk Misses	Total % Missed Items
0% cut-off point	42	1/0	0.3%
10% cut-off point	67	10/2	3.9%
20% cut-off point	83	31/8	12.6%
ERs	59	25/2	8.7%
New methodology	55	0/0	0.0%

Legend: CM: computer model; ERs: expert recommendations; IU: instrument usage.

3.4. Final Optimisation of SITs

The final outcomes were thus determined by using (1) the actual IU counted in the OR and (2) ERs, which were both integrated in the CM, with a cut-off point of 10%, followed by (3) a final check by the three gynaecologists and OR nurses. The total number of reusable instruments distributed across three trays decreased from 150 to 95 instruments, marking a reduction of 36.7%. Each individual tray achieved a reduction percentage between 30 and 40%. Figure 3 shows the instruments that were removed from the specific trays. The trays were then consolidated into two trays (gynaecology laparotomy (GL1 and GL2)). Overall, there was a weight reduction of 3.2 kg (31.3%) in instrumentation. The consolidation of instruments from three to two trays further reduced the weight by 1 additional kilogram (kg), bringing the total to approximately 4.2 kg.

Figure 3. Actual instrument reduction. Each picture shows the instruments that were kept on the **left** and the ones that were removed on the **right** (from **left** to **right**: basic tray, gynaecological tray, and oncological tray).

3.5. Evaluation of Endurance of New Composition of SITs

During the evaluation phase, the completeness of the SITs was observed. The seven remaining surgeries underwent direct evaluation by the trained author to assess the new SIT compositions, encountering no issues. The mean instrument use across all observed procedures increased from 28.4% (SD = 6.4%) to 46.5% (SD = 11.0%), without any instrument misses. It is important to note that these SITs are utilised for various procedures, resulting in varying types of instruments being used for each procedure. Furthermore, in the evaluation phase, 15 instruments were never used. However, of these 15 instruments, 9 instruments did have a 'veto' not to be removed. Following this, over a year-long period comprising 122 and 135 uses for GL1 and GL2, respectively, the SITs retained their composition without any new instrument requirements emerging.

4. Discussion

To optimise SITs, we combined two different methods and assessed the performance of a new combined set of SITs for over a year. The methodology reduces the number of instruments and the total weight, without risking the absence of vital instruments in subsequent procedures over a year.

To achieve maximum reduction potential safely in patients, both objective IU and subjective ERs are necessary. This is because reductions in SIT content solely based on an objective IU with a cut-off point of 0% are safe but do not utilise the full reduction potential. On the other hand, reductions in tray content relying solely on higher cut-off points or on ERs can yield similar reduction percentages as the combined methodology but may pose risks to patient safety. The results of these individual methods indicate a higher risk of instrument misses, potentially leading to unsafe situations during surgical procedures.

Although both individual methods (IU and ERs) aim to achieve optimal tray content and have similar reduction potentials, they diverge in suggesting which instruments should be removed. These discrepancies can ultimately lead to instances of missing instruments during surgical procedures. What could contribute to these differences is, first, that medical specialists may be hesitant to remove certain instruments. Disagreements may arise regarding these content wishes on the tray, resulting in more instruments than necessary remaining on it. Additionally, data might indicate occasional use of various instrument sizes, while in reality, according to interviewed specialists, only one or two sizes suffice.

Furthermore, upon observing the actual IU, we have noticed that many instruments are seldom or never utilised. Nevertheless, some of these instruments are critically necessary in scenarios involving bleeding or other medical emergencies. The absence of such instruments can significantly stress surgeons and lead to poor clinical outcomes, surgical errors, and extended surgical procedure times [12]. Therefore, categorising instruments between high- and low-risk categories assists in identifying those items that should be exempted from automatic removal. A solution to remove these high-risk items that are

sporadically used from the SIT altogether is to ensure they are present in the OR in separate laminate packaging. In this way, unnecessary cleaning and sterilisation are avoided without compromising patient safety.

Recent studies have explored the effects of reducing the number of surgical instruments on trays through various approaches. These include creating a model based on the probability of an instrument being used or employing real IU data integrated into a mathematical optimisation model [18,19]. Santos et al. [17] conducted a review of 48 papers, identifying 34 papers on expert analysis (EA), 9 papers on lean practices (LP), and 5 papers on mathematical programming (MP). However, to our knowledge, studies based on MP lack extended follow-up observations in real-world practice to assess the combined effects of tray combinations or the necessity of individually wrapped items. We combined ERs and real IU into a CM and observed the stability of the new optimised SIT. Notably, the following year required no changes due to missing instruments in the SIT. Our findings demonstrate that this approach maintained consistent SIT contents for one year post-transition. Furthermore, our focus extended beyond streamlining; we aimed to reduce the number of trays while ensuring they remained manageable for personnel. This strategy aimed to achieve optimal loading efficiency in both the washer/disinfector and the steriliser.

Surgical equipment accounts for a significant portion of the carbon footprint in surgeries, primarily due to the prevalence of disposable items [20]. Transitioning from disposable to reusable or hybrid equipment can positively impact the environment by reducing the carbon footprint [21–23]. However, the decontamination process of reusable surgical equipment represents a crucial environmental hotspot in its lifecycle. Therefore, it is imperative to optimise this process effectively and decrease the associated carbon footprint. It is essential to ensure maximal loading capacities for the washer/disinfector and steriliser, as partial loading increases the carbon footprint [4]. Merely streamlining SITs and reducing the number of surgical instruments in trays might unintentionally increase the carbon footprint; the preferable approach would be to reduce tray size or the overall number of trays [24]. In this study, we reduced the SITs from three to two, enabling additional trays to be loaded per machine slot. In this way, optimisation and reduction in SITs could eventually reduce the amount of slots. Furthermore, when too many high-risk instruments are excluded but available individually wrapped in laminate in the OR, this could lead to extensive use of individual instruments. Consequently, this will necessitate individual decontamination and packaging. By identifying and retaining high-risk items on the tray, even if occasionally used, this could result in a decrease in the use of individual instruments, thereby eliminating the need for individual decontamination. Collectively, these measures contribute to reducing the carbon footprint [4].

The impact of reducing SITs significantly affects personnel satisfaction and working conditions within the OR and CSSD, especially for perioperative nurses and CSSD employees. SITs stand as a primary contributor to the development of work-related musculoskeletal disorders [25,26]. A reduction in tray weight by more than 30% significantly improves ergonomics and elevates personnel satisfaction [7]. The reduction in instruments in this study led to a total weight decrease of 3.2 kg (31.3%), reducing the number of SITs from three to two, which is a positive outcome for employees handling SITs as they now need to lift fewer trays for the same surgery. While the overall number of trays decreased and, consequently, the total weight, the weight per tray remained unchanged.

The financial implications of tray optimisation have been thoroughly evaluated. Farrokhi et al. [27] developed a lean methodology, resulting in a 70% reduction. This lean approach consists of a 5S approach: sort, simplify, sweep, standardise, and self-discipline. Extrapolating this to the entire hospital led to approximately USD 2.8 million in cost savings within a year. Additionally, various studies have demonstrated reductions in instruments, leading to sustained cost reductions through alternative methodologies for SIT optimisation [11,28]. Hence, it can be concluded that tray optimisation consistently results in cost reductions.

The current study has several limitations. Most notably, none of the gynaecologists were blinded to the research objective. According to the Hawthorne effect, this lack of blinding might have induced behavioural changes aiming to influence research outcomes. These changes could involve unnatural instrument usage to ensure future availability. Nevertheless, the gynaecologists received specific instructions not to alter their regular instrument use in any way.

Secondly, the number of procedures observed to obtain actual IU in this research was relatively small. It is possible that seldom-used instruments were not recorded during this study. Nonetheless, the methodology has demonstrated its efficacy in a contemporary hospital environment and is also adaptable to other specialties. Moreover, the one-year follow-up period indicated no adjustments made due to missing instruments.

Lastly, the manual counting of IU in the OR introduces a risk of registration errors. Future work should focus on enhancing the scalability of the proposed methodology, which is currently limited unless data collection becomes automated, thereby reducing registration errors. To structurally improve the durability of the supply of sterile surgical instruments, continuous optimisation of SIT compositions based on current usage data is essential. These data should be automatically analysed, for instance, through video-based recognition and registration in the OR.

Subsequent research should prioritise achieving more substantial reductions by reducing tray size or quantity through integrating the clustering of similar instruments and incorporating replicated ERs in updated versions of the CM. This approach will help avoid more unnecessary resource use. The validation phase showed a considerable risk of missing instruments during surgery with higher cut-off points (10 or 20%). However, when combined with input from the gynaecologists, similar reductions were achieved without any missed instruments in subsequent procedures. Theoretically, artificial intelligence should be able to replicate expert input for larger datasets and potentially compose specific SITs for specific medical specialists or patients. The capability to automatically distinguish between specific instruments used for specific patients and track procedural phases through instrument usage is expected to be integrated into future ORs.

5. Conclusions

In conclusion, combining ERs with actual IU data results in a 36.7% reduction in instruments and a decrease from three to two trays, without any missed instruments in subsequent procedures. Although the individual methods show similar reduction potentials, there is a discrepancy in the recommendations for removing instruments from the SIT. Relying on a single method for SIT optimisation can lead to a higher likelihood of instrument misses, which poses a safety risk. We have thoroughly examined the potential for instrument misses, especially in relation to high-risk items that may be infrequently needed but are critical when required. Thus, combining both methods and taking high-risk items into account leads to an effective and patient-safe reduction. Moreover, during a one-year follow-up period, the tray contents remained unchanged. Implementing change in a complex environment like the OR requires time and should be executed gradually and in consultation with all involved parties. Combining IU and ERs using the proposed methodology can be safely implemented for patients, reducing unnecessary usage and enhancing sustainability.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/su16166953/s1: File S1: Boxplots; File S2; Comparison; File S3: EXCEL DATA; File S4: Excel data_English translation; File S5: Reduction_highrisk; File S6: Reduction_lowrisk; File S7: Step by step instruction MATLAB scripts.

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K.E.v.N.; Writing—original draft, K.E.v.N. and T.v.T.; Writing—review and editing, K.E.v.N., T.v.T., J.D. and A.C.v.d.E. All authors have read and agreed to the published version of the manuscript.

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