Journal Pre-proof

Research priorities in perioperative fluid therapy and hemodynamic monitoring: A Delphi Consensus Survey from the Fluid Therapy and Hemodynamic Monitoring Subcommittee of the Hemostasis, Transfusion Medicine and Fluid Therapy Section (SHTF) of the Spanish Society of Anesthesiology and Critical Care (SEDAR)

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Research Priorities in Perioperative Fluid Therapy and Haemodynamic Monitoring: A Delphi Consensus Study performed by the Fluid Therapy and Haemodynamic Monitoring Subcommittee of the Haemostasis, Transfusion Medicine and Fluid Therapy Section (SHTF) of the Spanish Society of Anaesthesiology and Critical Care (SEDAR)

Prioridades de investigación en términos de fluidoterapia perioperatoria y monitorización hemodinámica: encuesta de consenso Delphi del Subcomité de Fluidoterapia y Monitorización hemodinámica de la Sección de Hemostasis, Medicina Transfusional y Fluidoterapia (SHTF) de la Sociedad española de Anestesiología y Reanimación (SEDAR).

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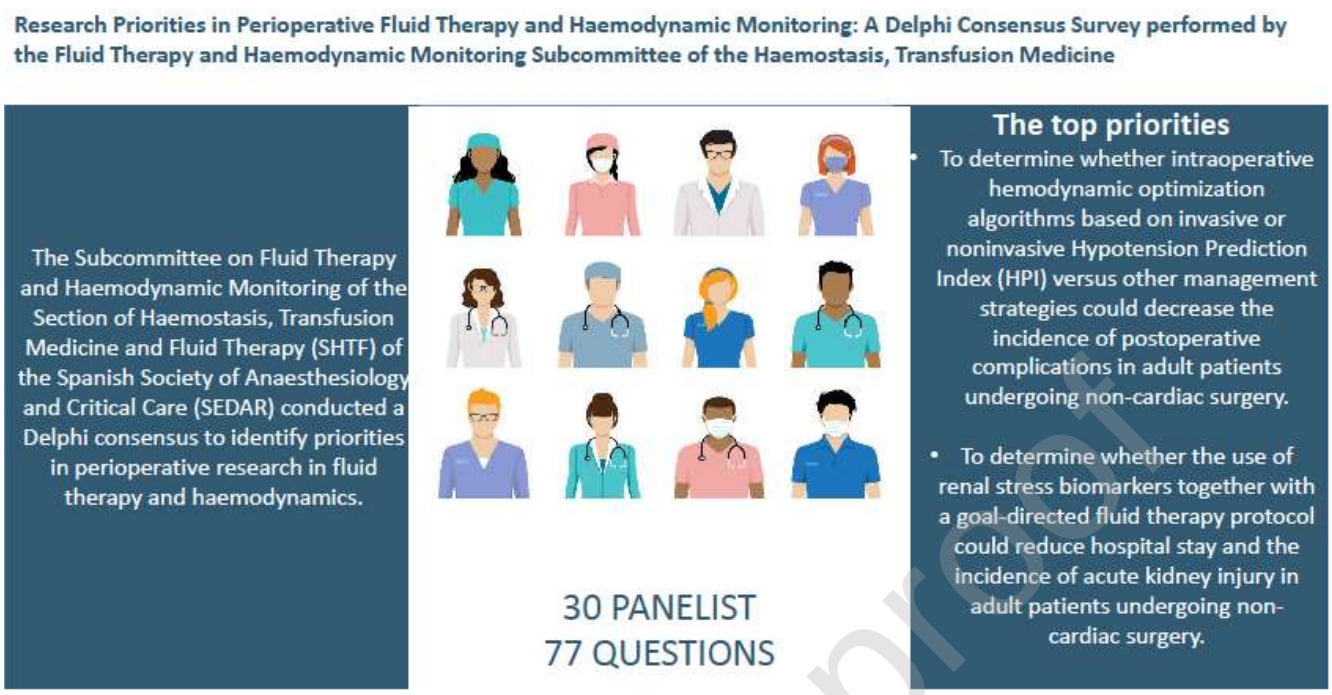
Graphical abstract



HIGHLIGHTS

- The Subcommittee on Fluid Therapy and Haemodynamic Monitoring of the Section of Haemostasis, Transfusion Medicine and Fluid Therapy (SHTF) of the Spanish Society of Anaesthesiology and Critical Care (SEDAR) conducted a Delphi consensus to identify priorities in perioperative research in fluid therapy and hemodynamics.
- Thirty expert panellists evaluated 77 questions

- Thirty-one questions reached consensus. Two of them reached the highest consensus and were considered a priority: To determine whether intraoperative haemodynamic optimization algorithms based on the invasive or non-invasive Hypotension Prediction Index versus other management strategies could decrease the incidence of postoperative complications. and whether the use of renal stress biomarkers together with a goal-directed fluid therapy protocol could reduce hospital stay and the incidence of acute kidney injury in adult patients undergoing non-cardiac surgery.

RESUMEN

Antecedentes: La investigación sobre fluidoterapia y monitorización hemodinámica perioperatorias es difícil y costosa.

Los objetivos del presente estudio fueron resumir y priorizar estas cuestiones, en orden de importancia investigadora.

Métodos: Cuestionario estructurado electrónico Delphi a lo largo de tres rondas entre 30 expertos en fluidoterapia y monitorización hemodinámica identificados a través del Subcomité de Fluidoterapia y Monitorización hemodinámica de la Sección de Hemostasis, Medicina Transfusional y Fluidoterapia de la Sociedad española de Anestesiología y Reanimación.

Resultados: Se identificaron 77 cuestiones, que se clasificaron en orden de priorización. Las

cuestiones se categorizaron en temas de cristaloides, coloides, monitorización hemodinámica y otros. Se categorizaron 31 cuestiones como de prioridad investigadora esencial, para determinar si los algoritmos de optimización hemodinámica intraoperatorios basados en el Índice de predicción de hipotensión invasivo o no invasivo frente a otras estrategias de manejo podrían reducir la incidencia de complicaciones postoperatorias, así como si el uso de biomarcadores del estrés renal junto con un protocolo de fluidoterapia dirigido por objetivos podría reducir la estancia hospitalaria y la incidencia de insuficiencia renal aguda en pacientes adultos sometidos a cirugía no cardiaca, lográndose el más alto consenso.

Conclusiones: El Subcomité de Fluidoterapia y Monitorización hemodinámica de la Sección de Hemostasis, Medicina Transfusional y Fluidoterapia de la Sociedad española de Anestesiología y Reanimación utilizará estos resultados para la realización de investigación.

PALABRAS CLAVE

Fluidoterapia; Hemodinámica; Investigación

Abstract

Background : Research in fluid therapy and perioperative hemodynamic monitoring is difficult and expensive. The objectives of this study were to summarize these topics and to prioritize these topics in order of research importance.

Methods : Electronic structured Delphi questionnaire over three rounds among 30 experts in fluid therapy and hemodynamic monitoring identified through the Fluid Therapy and Hemodynamic Monitoring Subcommittee of the Hemostasis, Transfusion Medicine and Fluid Therapy Section of the Spanish Society of Anesthesiology and Critical Care.

Results: 77 topics were identified and ranked in order of prioritization. Topics were categorized into themes of crystalloids, colloids, hemodynamic monitoring and others. 31 topics were ranked as essential research priority. To determine whether intraoperative hemodynamic optimization algorithms based on the invasive or noninvasive Hypotension Prediction Index versus other management strategies could decrease the incidence of postoperative complications. As well as whether the use of renal stress biomarkers together with a goal-directed fluid therapy protocol could reduce hospital stay and the incidence of acute kidney injury in adult patients undergoing non-cardiac surgery, reached the highest consensus.

Conclusions : the Fluid Therapy and Hemodynamic Monitoring Subcommittee of the Hemostasis, Transfusion Medicine and Fluid Therapy Section of the Spanish Society of Anesthesiology and Critical Care will use these results to carry out the research.

Keywords

fluid therapy; Hemodynamics; Research

NTRODUCTION

Postoperative complications after surgery are common, despite advances in health technology.(1,2) Fluid therapy guided by hemodynamic monitoring could potentially reduce postoperative complications.(3) However, despite the existence of multiple studies(4), recommendations(5) and guidelines(6), there is still great variability in fluid therapy administration, and very scarce use of hemodynamic monitoring.(7,8)

Collaborative national research in fluid therapy and hemodynamic monitoring requires effort, time, and financial resources. It is, therefore, necessary to define research priorities through a "context-sensitive" approach in order to improve perioperative outcomes.

The Delphi method has proven to be a reliable measurement tool to establish consensus and determine the appropriate direction of research efforts. This method seeks the opinion of a panel of experts to assess the degree of agreement and resolve disagreements on a particular question. (9)

This study aims to determine the main research priorities in the field of fluid therapy and perioperative hemodynamic monitoring in order to guide future initiatives from the Fluid Therapy and Hemodynamic Monitoring Subcommittee of the Haemostasis, Transfusion Medicine and Fluid Therapy Section (SHTF) of the Spanish Society of Anaesthesiology and Critical Care (SEDAR).

METHODS

We sent structured electronic Delphi questionnaires via email to blinded experts between June 2021 and December 2021, asking them to prioritise research topics relating to fluid therapy and haemodynamic monitoring in the perioperative setting. The primary goal was to identify a limited number of priority topics that can be investigated with support from SEDAR. The study is presented in accordance with Conducting and REporting of DElphi Studies (CREDES) recommendations.(10)

Study participants

Potential panel members were nominated by the 10 core members of the Fluid Therapy and Haemodynamic Monitoring Subcommittee of the SHTF of the SEDAR. To be considered, a nominee had to be an established researcher or active contributor to fluid therapy and/or haemodynamic monitoring education evidenced by authorship of education journal articles and textbooks, a director of fluid therapy and/or haemodynamic monitoring training programs or courses, a member of national or international anaesthesia or critical care education committees and/or anaesthesia education working groups, and have relevant clinical and/or academic expertise.

Each core member of the group freely nominated 2 experts. Reserve experts were selected to replace any nominees that did not respond to the invitation. The goal was to form a panel of at least 30 experts.

In order to avoid bias, we asked all panel members to state any potential conflicts of interest, although these were not necessarily exclusionary. However, all panel members had to consent to the publication of their conflicts of interest for the sake of transparency.

Nominees were sent an email explaining the purpose of the study and invited to participate. After reading the email and the study protocol, willing participants accepted the invitation and gave their informed consent to join the panel.

A coordinating group formed of JRM, MC and GY led the communication with the panel of experts, resolved any incidents arising, and drove the whole process.

Questionnaire development

The initial questionnaire was drawn up on the basis of a literature review. Different search strategies (last updated May 2021) were used to retrieve relevant randomized controlled trials (RCT), systematic reviews, and meta-analyses from MEDLINE Pubmed and The Cochrane Library databases. No date or language restrictions were applied. To reduce publication bias, abstracts were requested. Article were identified using the following search terms: randomized controlled trial, controlled clinical trial, meta-analysis, crystalloid, colloid, gelatine, Hydroxyethyl starch, blood pressure, postoperative complications, surgery, goal-

directed, goal oriented, goal target, cardiac output, cardiac index, DO2, oxygen consumption, cardiac volume, stroke volume, fluid therapy, fluid loading, fluid administration, optimization, optimization, supranormal, biomarkers.

Individual research priorities were rewritten in EPICOT (Evidence, Population, Intervention, Comparison, Outcome, Timestamp) (11) format, emphasizing the specific research questions that emerged from the available evidence after the initial literature search. The coordinating group drafted the initial research proposals in EPICOT format and arranged the items into several categories and groups to facilitate understanding. For most individual suggestions for non-cardiac surgery, for non-cardiac surgery in ERAS setting, and for cardiac surgery. Suggestions were grouped into clusters, and included: crystalloids, colloids, hemodynamic monitoring, and others, in which all panellists participated

Rounds

We defined a Delphi with a minimum of 2 rounds and a maximum of 4. In each round, panellists were given 2 weeks to answer the questionnaire. If no response was received within this time, they were contacted individually and allowed 10 more days. If no response was obtained after this period, the panellist was eliminated.

Round 1: screening

In Round 1, the initial list of EPICOT research topics was emailed to participants. A 9-point Likert scale was used to rate each topic. Panellists were asked to rate each topic on its own

merits, and not with respect to other topics. The Likert scale included text anchors on the following numerical scores to assist in rating: 1=not recommended for research, 4=some value for research, 7=important area for research, and 9=essential research. Panellists were also able to suggest other research topics in the free-text sections. Panellists returned their first round scores directly to the coordinating group. The aggregated scores of all panellists were used to calculate the mean score for each topic. The questionnaires were anonymous to reduce the dominance of the Delphi organizers and group compliance, and controlled opinion feedback was given. The coordinating group decided the feedback arrangements based on item responses and open-ended comments in each round. After each round, the data obtained were analysed and presented in a format that was easily interpretable to all panellists. The statistics shown to the panellists included measurement of central tendencies with dispersion, percentage, and frequency distribution (mean, median, the IQR). The controlled feedback allowed us to provide individual members with a clearer overview of group trends. Thresholds were predefined for each topic, and a median score of ≥7 by more than 70% of the participants allowed the topic to be included for final prioritization in Round 3. This was a strict threshold for selecting top-rated topics (with a minimum score of "important" or "essential"). Topics with a median score of ≤6 were excluded from further ranking. Background information of the experts participating in the study was collected in Round 1.

Prioritization of rounds 2 and 3

Free text topics contributed by each panellists were included in the following rounds. Topics with a mean score of 5 or more in the Round 1 were re-ranked in the Round 2 along with additional topics suggested by participants in the first round. To emphasize the prioritization of topics, panellists were reminded of the main objective of the consensus in each round. Panellists were asked to select the appropriate priority category, choosing a score within that category. In Rounds 2 and 3, participants were able to see the basic statistics (mean, median, IQR, and the absolute percentage of participants who rates the topic ≥6) of all research topics from Round 1, but were unaware of the individual responses; only the coordinating group had access to the individual scores. Items with a mean score of ≤6 were excluded.

In Round 3, the final round, panellists ranked the topics identified as highest priority in Round 1, i.e., a median score of ≥7 by more than 70% of participants. Similar instructions and Likert scales were used in this round. **Figure 1** shows the Delphi methodology. Consensus was defined as > 70% of participants agreeing/strongly agreeing or disagreeing/strongly disagreeing with a statement in Round 3. Finally, a virtual meeting of all panellists and coordinators was held to present the questionnaire results and show the priorities with the highest consensus. This was the first opportunity panellists had to interact. If there was more than 1 priority with highest relevance and consensus, the panellists and study steering committee decided which would have the highest priority for research.

For the purpose of external validation, the final draft of the study was reviewed and approved by an external authority (DE) prior to publication and dissemination.

RESULTS

Thirty experts were invited to participate by email; 28 (93.3%) accepted the invitation, and 2 more panellists were brought in to form a panel of 30 experts. All panellist completed the Round 1 and 2 questionnaires (100% response).

Background information on the expert panellists

The pane consisted of 7 (23.3%) women and 23 (76.6%) men; 3 (10%) are intensivists and 27 (90%) anaesthesiologists; 9 (30%) are heads of departments and 20 (66.6%) are consultants; 1 (3%) resident was included. The mean age of the panellists was 45 (standard deviation [SD] 9.8) years, with a mean of 22.5 (9.5 SD) years worked. Twenty-three (76.6%) panellists currently work in tertiary care hospitals, while the rest work in smaller centres. All panellists work in urban hospitals.

The organizing committee included 60 questions in Round 1, classified into 4 groups: crystalloids (n=14), colloids (n=16), haemodynamic monitoring (n=19) and others (n=11).

Forty-four (77.3%) questions were considered a research priority. In this round, the group suggested 33 questions, which were included in Round 2.

In Round 2, 77 topics were ranked **(Supplementary Table),** of which 57 (74%) were considered as priorities. In Round 3, 31 questions achieved consensus, and 2 of them reached the highest priority. The results are summarized in **Figure 2**. The 10 most relevant priorities for the expert panel are shown in **Table 1.**

The top priorities with greatest consensus were:

1. To determine whether intraoperative hemodynamic optimization algorithms based on invasive or non-invasive Hypotension Prediction Index (HPI) versus other management strategies could decrease the incidence of postoperative complications in adult patients undergoing non-cardiac surgery.
2. To determine whether the use of renal stress biomarkers together with a goal-directed fluid therapy protocol could reduce hospital stay and the incidence of acute kidney injury (AKI) in adult patients undergoing non-cardiac surgery.

DISCUSSION

The research priorities shown in this study represent the consensus of the Fluid Therapy and Monitoring Subcommittee of the SHTF of the SEDAR for perioperative research in fluid therapy and perioperative haemodynamic monitoring. This initiative brought together a wide range of clinicians from different hospitals, and is sensitive to the challenges and needs of perioperative research in Spain.

The participants in this survey could be considered the ideal group for defining a research protocol, but it is equally true that many of us have conflicts of interest. We decided to conduct this survey to maximize transparency in selecting research topics, not only because of our potential conflicts of interest but also because of the industry's interest in facilitating

certain topics. Conducting this survey within SEDAR allows the topics agreed upon to be promoted and researched, and makes it simpler to obtain the necessary research funding. The highest priority questions might not be related to known clinical dilemmas with conflicting evidence; instead, they were related to the application of new technologies that have the potential to influence patient outcomes but lack sufficient supporting evidence. Determining whether intraoperative haemodynamic optimization algorithms based on invasive or non-invasive HPI versus other approaches to decrease the incidence of postoperative complications in adult patients undergoing non-cardiac surgery was one of the two topics that achieved greatest consensus among panellists. Intraoperative hypotension has been associated with poor postoperative outcomes (12), including AKI and myocardial injury (13). The use of HPI algorithms has been shown to reduce the incidence of intraoperative hypotension (14), but there is no firm evidence that they improve postoperative outcomes. The question of whether the use of renal stress biomarkers in conjunction with a goal-guided fluid therapy protocol can reduce hospital stay and the incidence of AKI in adult patients undergoing non-cardiac surgery proved to be the other issue with the greatest consensus. Though scarce, there is some evidence that this approach can reduce postoperative AKI. (15) At the meeting following completion of the Delphi rounds, the panel considered that on the basis of feasibility, relevance, and the existence of similar studies actively recruiting patients, only one of the two studies considered equally important by the panel could initially be

conducted. RCTs (NCT05105105477, NCT04647396) are actively recruiting patients for studies in both topics, and for this reason the panel decided that the first study promoted by the Subcommittee on Fluid Therapy and Monitoring would be to determine whether an intraoperative haemodynamic optimization algorithm with invasive or non-invasive HPI would reduce the incidence of postoperative complications in adult patients undergoing non-cardiac surgery.

The panel did not consider research into crystalloids or colloids to be a priority at the moment, despite ongoing controversies surrounding this topic. (16) While from a physiologic standpoint the use of balanced crystalloids should improve postoperative outcomes compared to 0.9 saline(17), this has not been widely demonstrated in randomized clinical trials, and the evidence from critical care is conflicting. Similarly, some authors have reported slight improvements in analytical and fluid balance when comparing hypotonic crystalloids with isotonic crystalloids, due to their lower sodium and potassium content; however, no RCTs have shown their benefit.(18) The panel did not consider it important to investigate whether liberal versus restrictive maintenance fluid therapy was a priority, despite the controversy following the RELIEF study.(19) Neither was colloid research considered a priority, despite this being the subject of extensive investigation, but again, without conclusive results.(20)

There are limitations to this Delphi research priority-setting process. The priority list reflects the opinions of perioperative physicians, but does not include input from other members of the perioperative process (surgeons, nurses, managers), or service users (patients and caregivers). Despite this, both the patient experience and postoperative outcomes featured prominently in this research priority setting process.

CONCLUSIONS

The findings of this study have the potential to develop far-reaching perioperative research by highlighting the areas in which research is most needed. We urge funding scientific societies and public agencies to consider promoting these perioperative research priorities. Furthermore, we encourage partnerships with members involved in perioperative patient care to advocate for these priorities and funding requests. These results set the SEDAR agenda for research in fluid therapy and hemodynamic monitoring in the immediate future, and this in turn will promote the development, funding, and performance of new studies in areas with the greatest need for investigation and the greatest potential impact on healthcare.

AUTHORS' CONTRIBUTION

All authors were involved in conception and design of the study, and interpretation of the data; drafting the article; and final approval of the manuscript.

FUNDING

There was no source of funding

CONFLICT OF INTEREST

JRM: Honoraria for conferences, courses and research from Edwards Lifesciences; honoraria for conferences from Biomerieux and Fresenius Kabi. MJC: Honoraria for courses and conferences from Baxter, Vifor Pharma, Ferrer and MSD. CA: Honoraria for conferences, courses and research from Fresenius Kabi, Ferrer and Vifor Pharma JAC: Honoraria for courses from Vifor Pharma, Glaxo Smith Kline and MBA. JMAI: Honoraria for lectures from Vygon and Baxter. HA: Funding for symposia by LiDCO and Edwards Lifesciences. Medical Affairs Manager at Getinge since October 2021. MB: Honoraria for conferences from Baxter. ECP: Honoraria for conferences, courses and research from Edwards Lifesciences; honoraria for conferences from BRAUN. RF: Honoraria for conferences from Baxter and Fresenius Kabi. PGM: Honoraria for conferences from Baxter. IJL: Honoraria for courses and conferences from Edwards Lifesciences. JJP: Honoraria for conferences from MSD, Baxter and Fresenius Kabi. JLP: Honoraria for conferences from Baxter and Fresenius Kabi JVL: Honoraria for courses, research, and conferences from Edwards Lifesciences and bioMérieux. Honoraria for courses and conferences from Fresenius

Kabi, Grifols, Vifor Pharma and Baxter. MIMG: Honoraria for conferences, courses and research, and acted as medical advisor for Edwards Lifesciences. MdN: Honoraria for conferences, courses and travel expenses from Baxter. Honoraria for courses, research and conferences from Edwards Lifesciences. Honoraria for research from Ferrer and Pfizer JTR: Honoraria for courses and conferences from Baxter and Edwards Lifesciences. AP: Honoraria for conferences, courses and research from Edwards Lifesciences; honoraria for conferences from MSD and Fresenius Kabi. RUO: Honoraria for courses and conferences from Baxter. JGF: Honoraria for conferences GE, Dräger and Getinge. FCT, FCD, IG, JM, IM, FMF, JMR, FR, GY, AZV and DE have nothing to declare.

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FIGURE LEGENDS

Figure 1: Delphi process

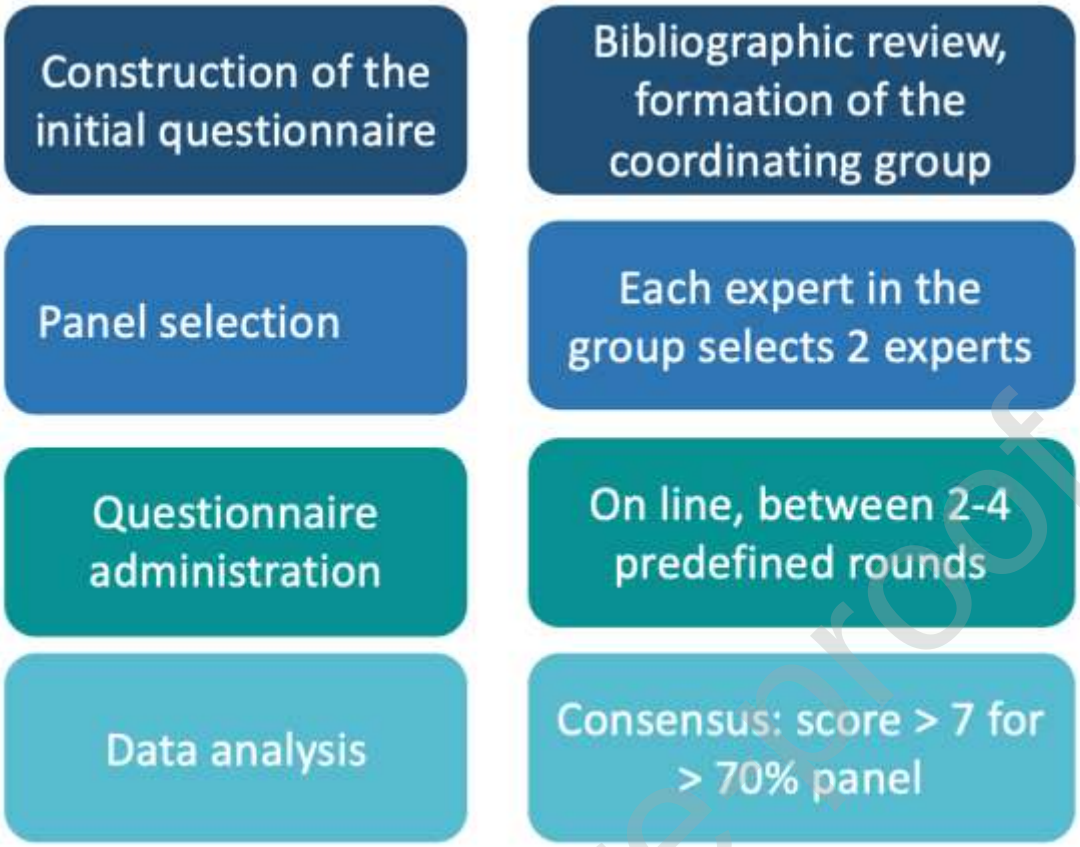

Figure 2: Results summary

LEYENDAS DE FIGURAS

Figura 1: Proceso Delphi

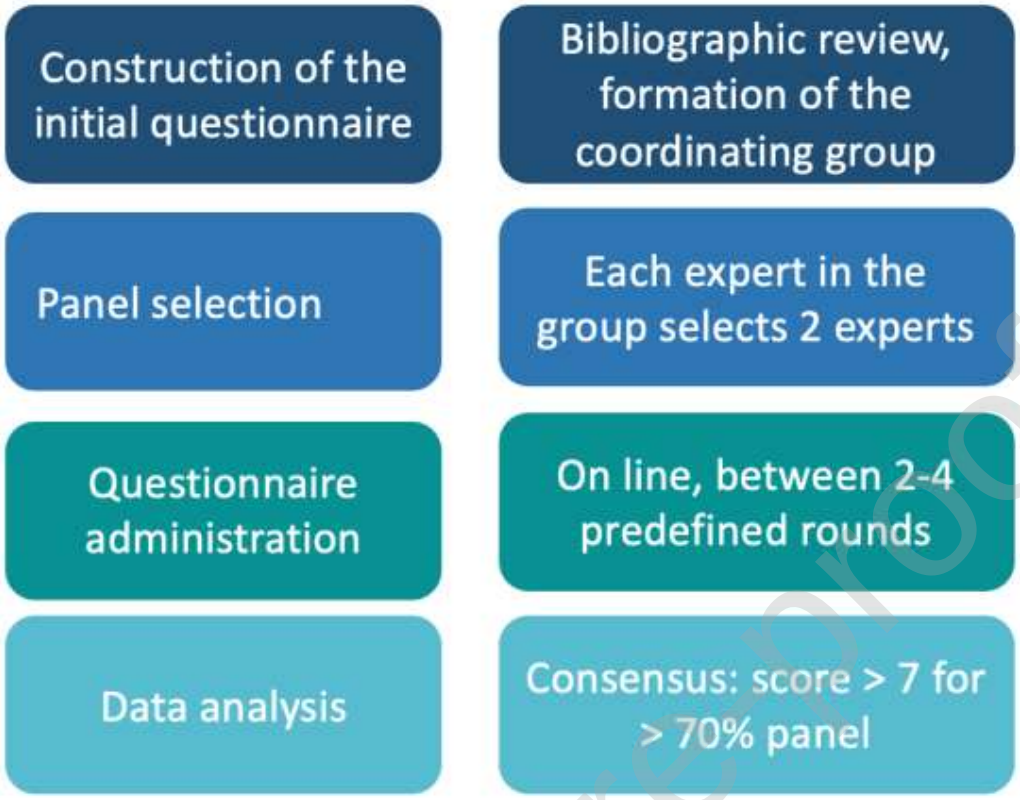

Figura 2: Resumen de los resultados

Table 1: Top ten research priorities

Item	Agreement
The comparison of intraoperative hemodynamic optimization algorithms based on invasive or non-invasive Hypotension Prediction Index (HPI) is a priority to reduce the incidence of postoperative complications in adult patients undergoing non-cardiac surgery.	96.3
It is a priority to determine whether the use of renal stress biomarkers together with a goal-guided fluid therapy protocol can reduce hospital stay and the incidence of acute kidney injury in adult patients undergoing non-cardiac surgery.	96.3
The comparison between intraoperative versus intra-postoperative hemodynamic optimization algorithms is a priority to reduce the incidence of postoperative complications in adult patients undergoing major non-cardiac surgery.	92.6

The comparison of intraoperative hemodynamic optimization algorithms based on flow (stroke volume optimization) vs pressure (blood pressure optimization) is a priority to reduce the incidence of postoperative complications in adult patients undergoing non-cardiac surgery.	92.6
The comparison of intraoperative hemodynamic optimization algorithms based on invasive or non-invasive Hypotension Prediction Index (HPI) is a priority to reduce the incidence of postoperative complications in adult patients undergoing non-cardiac surgery in an ERAS environment.	88.9
It is a priority to determine whether the use of renal stress biomarkers together with a goal-guided fluid therapy protocol can reduce hospital stay and the incidence of acute kidney injury in adult patients undergoing non-cardiac surgery in ERAS settings.	88.9
It is a priority to determine if it is possible to identify at-risk patients using parameters derived from advanced hemodynamic variables derived from advanced non-invasive monitoring (i.e.: Clearsight, including cardiac output, stroke volume or combinations)	85.2
The comparison between balanced and unbalanced crystalloids is a priority to	81.5

reduce the incidence of postoperative kidney injury in adult patients undergoing major non-cardiac surgery.	
The comparison between intraoperative compared to intra-postoperative hemodynamic optimization algorithms is a priority to reduce the incidence of postoperative complications in adult patients undergoing major non-cardiac surgery in an ERAS setting.	81.5
The comparison of flow / pressure-based intraoperative hemodynamic optimization algorithms with mean arterial pressure targets of 65 mmHg or <20% baseline is a priority to reduce the incidence of postoperative complications in adult patients undergoing non-cardiac surgery.	81.5