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REVIEW ARTICLE

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Patient and public involvement in contemporary large intensive care trials: A meta-epidemiological study

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Abstract

Background: Patient and public involvement in randomised clinical trials has received increased focus, including in intensive care trials, but the frequency, method and extent is unknown. This meta-epidemiological study investigated patient and public involvement in contemporary, large ICU trials.

Methods: We systematically searched PubMed for large (≥225 randomised patients), contemporary trials (published between 1 January 2019 and 31 January 2022) assessing interventions in adult patients in ICU settings. Abstracts and full-text articles were assessed independently and in duplicate. Data were extracted using a predefined, pilot-tested data extraction form with details on trials, patient and public involvement including categories and numbers of individuals involved, methods of involvement, and trial stage(s) with involvement. Trials authors were contacted as necessary.

Results: We included 100 trials, with 18 using patient and public involvement; these were larger and conducted in more centres than trials without patient and public involvement. Among trials with patient and public involvement, patients (in 14/18 trials), clinicians (13 trials), and family members (12 trials) were primarily involved, mainly in the development of research design (15 trials) and development of research focus (13 trials) stages and mostly by discussion (12 trials) and solo interviews (10 trials). A median of 65 individuals (range 1–6894) were involved.

Conclusions: We found patient and public involvement in a fifth of large, contemporary ICU trials. Primarily patients, families, and clinicians were included, particularly in the trial planning stages and mostly through interviews and discussions. Increased patient and public involvement in ICU trials is warranted.

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KEYWORDS
clinical trial, community participation, critical care, patient participation, randomised controlled trial

Editorial Comment

This systematic review presents an overview of the degree so far of input from patient interests to interventional studies of intensive care treatments. The authors found that only in a small portion of these studies patient interest and input could be found for the study planning, at least for published ICU trials.

1 | INTRODUCTION

In recent years, there has been increased focus on patient-centred or patient-important outcomes, and patient and public involvement has been suggested to support this process.[1] Inclusion of patients' preferences and opinions in clinical research has previously been limited,[2] and thus the research agenda has primarily been set by academia, industry, and other non-patient and non-public stakeholders.[3] Several initiatives have been established to facilitate patient and public involvement,[4] including *Involve*, a public participation charity in the United Kingdom (www.involve.org.uk), and the *Patient-Centered Outcomes Research Institute (PCORI)*, an independent, non-profit research organisation in the United States (www.pcori.org).

Patient and public involvement in research in the intensive care unit (ICU) setting is complex because of the nature of critical illness[5] and the high mortality in critical illness. Patients in the ICU setting may, however, be more susceptible to adverse effects of interventions, which together with the high resource use makes involvement important. Therefore, involving survivors, relatives and other patient advocates is important to ensure that trials provide value for future patients. Patient and public involvement in all stages of research can help to reveal new areas worthy of the focus of trialists, enhance the relevance and quality of future research, select, and prioritise patient-important outcomes, and improve dissemination to all relevant stakeholders, including patients and members of the public.[4]

Patient and public involvement can be used in different stages within the research process as defined by Pii and colleagues[4]: (1) development of research focus, (2) development of research design, (3) recruitment, (4) data generation, (5) data processing, and (6) research dissemination. Patient and public involvement can be achieved with a wide range of methods and approaches, including traditional qualitative and quantitative methods (e.g., interviews, focus groups, surveys), as well as more comprehensive techniques such as Delphi processes or the James Lind Alliance Priority Setting Partnerships method.[4,6,7]

With this meta-epidemiological study, we aimed to investigate the use of patient and public involvement in contemporary, large randomised clinical trials (RCTs) conducted in the ICU setting, including how often patient and public involvement occurred, which groups were consulted, how involvement was done, at what stage in the trial process it occurred, and how many patient/public representatives were consulted.

2 | METHODS

2.1 | Study design

This meta-epidemiological study of contemporary, large RCTs conducted in the ICU setting was conducted according to a published protocol[8] and is reported according to the reporting guidelines for meta-epidemiological studies by Murad and Wang,[9] an adaptation of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[10] specifically tailored for meta-epidemiological studies (checklist included in the supplement S1). No ethical approvals were relevant for this study.

2.2 | Eligibility criteria

We included data from large, contemporary RCTs conducted in an ICU setting with results reported from 2019 and onwards. Large RCTs were defined as RCTs with ≥225 randomised participants, which was the 75% percentile of sample sizes based on a previous meta-epidemiological study of 604 ICU RCTs conducted between 1977 and 2018;[11] large RCTs were eligible regardless of the number of centres they were conducted in. We focused solely on large RCTs, as their results are more likely to change clinical practice and as we expected that patient and public involvement would be very infrequent in smaller RCTs (including feasibility/pilot trials and early-phase trials). Similarly, we solely focused on RCTs published in 2019 or later to ensure contemporary results. In addition to the temporal and sample size-based restrictions, we only included RCTs that assessed interventions in adult patients in an ICU setting, as defined by the authors. RCTs that included both adults and children or where this was unclear were eligible if >50% included patients could be reasonably assumed to be ≥18 years based on available descriptive data. Similarly, we assumed that RCTs were conducted in an ICU setting if >50% of patients received interventions typically restricted to the ICU (e.g., continuous use of vasopressors/inotropes, mechanical ventilation, or invasive monitoring not restricted to the operating room). We excluded RCTs where the intervention primarily occurred outside the ICU, even if patients were subsequently admitted to the ICU (e.g., perioperative trials with subsequent ICU admissions, but interventions primarily taking place pre- or intra-operatively).

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2.3 | Search strategy and study selection

We searched PubMed on 13 July 2021 and updated the search on 31 January 2022 using a search string including keywords for intensive care and RCTs in titles/abstracts or subject headings, filtered to studies conducted in humans and published online or in print from 1 January 2019 and onwards (full search string included in the supplement S1).

We used Covidence (www.covidence.org) for screening and study selection. Abstracts and titles were screened for eligibility independently and in duplicate, as were full texts, with discrepancies resolved through discussion or by involvement of a third author.

2.4 | Outcomes

The primary outcome was the proportion of included RCTs that used patient and public involvement, as defined in accordance with Pii and colleagues[4] or by the included trials.

Secondary outcomes assessed included the following:

1. Which groups were consulted (patients, families, clinicians, patient organisations, others [e.g., legal representatives and non-patient members of the public])?
2. How were the opinions of patients and their representatives collected (as defined by Pii and colleagues[4]: individual interviews, group interviews, surveys, focus groups, workshops, Delphi processes,[6] discussions, Priority Setting Partnerships/the James Lind Alliance method)?[7]
3. At what stage of the process was patient and public involvement used (as defined by Pii and colleagues[4]: development of research focus, development of research design, recruitment, data generation, data processing, research dissemination)?
4. How many individuals (or organisations) were consulted in total?

2.5 | Data extraction and management

Data from eligible trials were extracted independently and in duplicate using a pre-defined[8] electronic extraction form (supplement S1), pilot tested by two authors on the first 10 trials. Discrepancies were resolved by discussion or involving a third author.

The following characteristics were extracted: trial acronym or first author name, year of publication, countries, number of centres, trial size, funding statements and classification (public, industry, philanthropic, other, none, or not stated), interventions assessed and classification (drug, device, management, or combinations based on previous definitions, as previously defined[8,11,12]), disease area, and whether patient and public involvement was mentioned in the manuscript (including supplements and referenced protocols). For trials that mentioned patient and public involvement, we extracted additional information on the secondary outcomes, as defined in the secondary outcomes above.

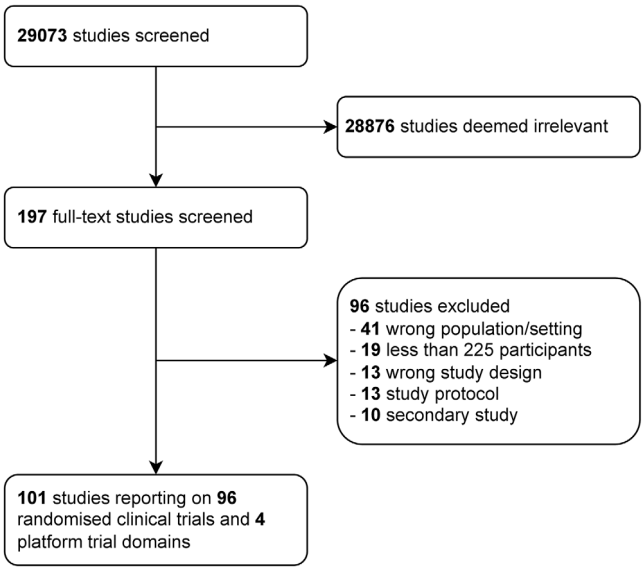

FIGURE 1 Inclusion flowchart. Of the 101 studies included, two reports were on the same factorial trial (INSPIRATION/INSPIRATION-S; counted as one trial in the analyses and presentation), and four separate domains from a platform trial were included (REMAP-CAP; counted as four separate trials in the analyses and presentation). 'Wrong study' design covers full-texts that were not randomised clinical trials.

2.6 | Dealing with missing data

For RCTs where patient and public involvement was not mentioned or where this was too sparsely detailed to classify the patient and public involvement according to our secondary outcomes, we contacted corresponding authors by email at least twice with at least 14 days in between. If no response was obtained, we assumed that the RCTs in question did not use patient and public involvement.[8] The final proportions of missing data for all variables are presented along with the results.

2.7 | Statistical analysis

Descriptive trial-level data for all trials and stratified by the use of patient and public involvement were summarised using simple descriptive statistics, with categorical data summarised using numbers and percentages, and numerical data summarised using medians, interquartile ranges (IQRs) and full ranges. Details on patient and public involvement in trials using patient and public involvement were summarised similarly. Separate summaries according to intervention type, number of centres (single- vs. multi-centre RCTs), and type of funding were pre-planned,[8] but not presented due to the relatively limited number of RCTs using patient and public involvement with most being either in the same category or with multiple categories containing very few trials. Analyses were conducted using R version 4.2.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

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TABLE 1 Trial-level data stratified by the use of patient and public involvement

Characteristic	All trials ($n = 100$)	Trials without patient and public involvement ($n = 82$)	Trials with patient and public involvement ($n = 18$)
Year of publication	2020 (2019–2021) [2019–2021]	2020 (2019–2021) [2019–2021]	2021 (2019–2021) [2019–2021]
Countries (n)[a]	1 (1–2) [1–32]	1 (1–1) [1–32]	2 (1–7) [1 - 26]
Multicenter trial	78 (78.0%)	61 (74.4%)	17 (94.4%)
Number of centres	15 (3–35) [1–263]	12 (1–31) [1–263]	48 (16–74) [1–256]
Trial size (number of patients randomised)	528 (323–1002) [195–26,982]	497 (308–812) [195–26,982]	1076 (417–2460) [232–4000]
Intervention type[b]			
Drug	47 (47.0%)	37 (45.1%)	10 (55.6%)
Management	36 (36.0%)	29 (35.4%)	7 (38.9%)
Device	17 (17.0%)	16 (19.5%)	1 (5.6%)
Funding[c]			
Industry	28 (28.0%)	22 (26.8%)	6 (33.3%)
Public	74 (74.0%)	58 (70.7%)	16 (88.9%)
Philanthropic	15 (15.0%)	10 (12.2%)	5 (27.8%)
Other	2 (2.0%)	2 (2.4%)	0 (0.0%)
None	8 (8.0%)	8 (9.8%)	0 (0.0%)
Not stated	2 (2.0%)	2 (2.4%)	0 (0.0%)

Note: Trial-level data stratified by the use of patient and public involvement or not. Numeric data are presented as medians (interquartile ranges) [full ranges], while categorical data are presented as numbers (percentages). There were no missing values for these data.

[a]Specific countries listed in the supplement.

[b]No trials were categorised as combinations of the three intervention types.

[c]Many trials received multiple categories of funding; the percentages thus do not sum to 100.

3 | RESULTS

We screened 29,073 studies and included 101 publications reporting on 96 RCTs (including two reports on the same factorial trial, considered as one trial) and four domains of a platform trial (considered as separate trials) (Figure 1); of these 100 trials, 18 trials (18%) used patient and public involvement.

Characteristics of the included trials stratified by the use of patient and public involvement is presented in Table 1. Overall, most trials were conducted in few countries (median 1, IQR 1–2), most were multicentric (78%), and a median of 528 patients (IQR 323 to 1002) were included. Most interventions were drug interventions (47%), and 74% of trials received public funding while 28% received industry funding. Trials using patient and public involvement were generally larger and conducted in more centres than trials not using patient and public involvement.

Details on patient and public involvement in trials using patient and public involvement are summarised in Table 2. Patients (in 14–18 of trials using patient and public involvement), clinicians (13 trials), and family members (12 trials) were primarily involved. The primary methods used were discussion (12 trials) and solo interviews (10 trials), and patient and public involvement was mainly used in the development of research design (15 trials) and development of research focus (13 trials) stages. A median of 65 individuals (range 1 to 6894) were asked. Detailed information on all included trials is presented in the supplement S1.

Extensive and especially noteworthy patient and public involvement occurred in some trials (supplement S1). The Magic Bullet trial,[13] which compared colistin with meropenem for ventilator-associated pneumonia, involved 265 individuals in most stages of the trial, including patients, family members, patient organisations, and clinicians through solo interviews, group interviews and workshops. The POPPI cluster-trial,[14] which assessed a nurse-led preventive, complex psychological intervention to reduce post-traumatic stress disorder in patients receiving advanced intensive care, involved 382 individuals in a comprehensive patient and public involvement program informing most stages of the trial. This patient and public involvement program included patients, family members, patient organisations, clinicians and others through solo interviews, group interviews, focus groups, discussions, James Lind Alliance Priority Setting Partnerships, and other methods. The PROSPECT trial,[15] which compared probiotics with placebo for preventing ventilator-associated pneumonia and other infections in critically ill mechanically ventilated adults, involved 550 individuals in an extensive patient and public involvement program informing all stages of the trial, including patients, family members, and clinicians through solo interviews, surveys, discussion, and other methods. Finally, the REMAP-CAP platform trial (with four separate platform domains assessing different interventions included[16–20]) involved >6890 individuals in a comprehensive patient and public involvement program preparing the overall platform trials and the individual domains, including patients, family members,

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TABLE 2 Details on patient and public involvement in trials with patient and public involvement

Characteristic[a]	Trials with patient and public involvement ($n = 18$)
Who was asked?	
Patients	14 (77.8%)
Family	12 (66.7%)
Clinicians	13 (72.2%)
Patient organisations	6 (33.3%)
Other[b]	6 (33.3%)
How were they asked?	
Solo interview	10 (55.6%)
Group interview	4 (22.2%)
Survey	5 (27.8%)
Focus group	6 (33.3%)
Workshop	1 (5.6%)
Delphi	0 (0.0%)
Discussion	12 (66.7%)
James Lind Alliance method	2 (11.1%)
Other[c]	9 (50.0%)
At which stage(s) were they asked?	
Development of research focus	13 (72.2%)
Development of research design	15 (83.3%)
Recruitment[d]	9 (50.0%)
Data generation	5 (27.8%)
Data processing	8 (44.4%)
Dissemination	9 (50.0%)
How many were asked?	65 (9–2136) [1–6894][e]

Note: Numeric data are presented as medians (interquartile ranges) [full ranges], while categorical data are presented as numbers (percentages). Definitions of methods and trial stages are according to Pii and colleagues.[4]

[a]As trials included multiple categories, the percentages under each heading to not sum to 100.

[b]Including legal representatives and non-patient members of the public.

[c]Details included in the supplement.

[d]Defined according to Pii and colleagues;[4] includes both development of recruitment/retention strategies and participation in recruiting research participants.

[e]Missing/unclear in two trials (11.1%); no data were missing for any of the other characteristics.

clinicians, and others through focus groups, solo interviews, survey, discussion, and other methods.

4 | DISCUSSION

We examined the use of patient and public involvement in large, contemporary trials in the ICU setting and found patient and public involvement in a fifth of the included trials. Primarily patients, family members, and clinicians were involved, most often in the trial design stages and primarily through discussion or interviews.

The 18 trials included that used patient and public involvement altogether involved representatives in all research stages, but mostly in the development of research design and development of research focus stages, which is a common finding in research regarding patient and public involvement.[1,21] Interestingly, many of the included trials used patient and public involvement all the way through the research process and half also at dissemination of results. This may be because patient and public -representatives were included in the trial management groups or because the representatives were recruited from patient organisations helping to disseminate results to their affiliates.

Some of the included trials stated that clinicians were involved as patient and public involvement. The role of these clinicians could not be determined in all trials. In many cases, trialists are both researchers and clinicians and when clinicians were explicitly stated to be part of the trial groups or steering committees in conventional trial management roles, this was not considered patient and public involvement. On the contrary, when clinicians were asked to give feedback to trial design or methods, this was considered patient and public involvement, and where it was unclear if there was overlap, we included clinicians in our results.

The most common method of involvement was solo interviews. This was surprising because it is more resource demanding than group interviews, focus groups, or surveys. Most trials used multiple methods of inclusion, but only one (the INTEREST trial[22]) used solo interviews as the only method for patient and public involvement. This trial included 10 family members as patient and public representatives.[22] For trials using multiple methods, we–in most cases–do not have data regarding how many were asked using which method. It is not surprising, though, that the REMAP-CAP platform trial (with four domains included) which had the most patient and public representatives used surveys as one of multiple methods to gather input.[16–20]

Much of the previous research in patient and public involvement was done in groups with chronic conditions with a well-established network of patients and families.[1,21] Patients in the ICU may be more heterogenous than other groups. Furthermore, because of the acute nature of critical illness, it is impossible to recruit patients before they become critically ill. This means that all patients and families have had a life-changing event before being able to participate in research. For this reason, they may need time to heal physically and emotionally and some have persistent cognitive issues, limiting their ability to participate in large groups or for longer periods.[23–25]

4.1 | Strengths and limitations

This meta-epidemiological study has several strengths. First, we used a broad search strategy, including a diverse range of interventions and restricted the search to recent trials to ensure contemporary relevance of the results, and all screening and data extraction was done independently and in duplicate. Second, we contacted trial authors where necessary, which increased data correctness even if patient and public involvement was not mentioned in the primary report, its supplements, or the protocol. This was the case for several trials that

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used patient and public involvement, possibly because reporting patient and public involvement is not mandated by in the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines[26] or most journals. By contacting authors, we have thus limited the potential of underreporting of patient and public involvement influencing our results. Third, the study was conducted according to the published protocol with clear definitions of the categories of interest.[8]

This study also has some limitations. First, by restricting inclusion to newer, larger trials we were not able to assess trends in patient and public involvement over time. Larger and more well-conducted trials may be more likely to include patient and public involvement and our sample is therefore likely not representative for smaller ICU RCTs. This choice was deliberate, as larger trials are more likely to change practice. For this reason, patient and public involvement may be less relevant in smaller trials (including exploratory, early-phase trials and pilot/feasibility trials) and assessing patient and public involvement in larger trials thus seemed more relevant.[8] Second, we extracted a limited number of trial characteristics, and we did not assess trial quality or risk of bias. This was chosen as risk of bias pertains to evaluation of the effect of the intervention, something which was not of interest in the current study. Third, while we classified patient and public involvement in pre-specified categories, there were some borderline cases that could possibly be classified differently. Fourth, we counted separate domains from the REMAP-CAP platform trial[16–20] as separate trials due to their size and their resemblance in scope to individual RCTs; while patient and public involvement in REMAP-CAP included domain-specific patient and public involvement, it also included patient and public involvement general to the full platform trial. There is thus substantial overlap between patient and public involvement in the four domains included and, consequently, the four platform domains could also have been classified as a single trial. Fifth, while the search was comprehensive and many trials screened, the overall number of trials included is relatively small, with few trials using patient and public involvement. Some estimates from this study are thus based on relatively few trials, which should be kept in mind when interpreting the results. Due to the a priori relatively limited expected number of trials employing patient and public involvement,[8] we only used descriptive statistics to summarise the data. For the same reason detailed analyses in different subgroups of trials were not feasible. Sixth, the search was last updated in January 2022; however, we believe that the included trials are sufficient to provide an adequate, contemporary overview of patient and public involvement in large ICU trials. Seventh, the search was restricted to a single database (PubMed); we expect that most large trials conducted in critically ill patients are published in journals indexed in PubMed, but we cannot exclude the possibility that additional, relevant trials had been identified if more databases had been searched. Eighth, while we contacted study authors multiple times and in a systematic manner in trials where the use (or lack of) patient and public involvement was unclear, there is still a risk of underestimating the use of patient and public involvement, as some corresponding authors may not have seen or replied to our emails. Finally, we did not extract or request data from the trial authors about how much influence patient and public involvement had on the design, conduct, reporting, dissemination or other aspects of the trials or which challenges were faced in the implementation of patient and public involvement; these topics may be difficult to quantify but are worthy of further study.

5 | CONCLUSIONS

We found patient and public involvement in a fifth of large, contemporary RCTs conducted in ICU settings. Involvement was seen in all trial stages, but most often in the development of research focus and development of research design stages. Primarily patients, family members, and clinicians were included, mainly through interviews and discussions.

Focus on increasing patient and public involvement in general and in trial stages beyond the early stages seem warranted to ensure that the largest trials conducted in the ICU considers the interest of patients, their representatives, and the public, to increase the likelihood that trials will benefit patients and society. Requirements by journals and in reporting checklists to report on patient and public involvement use in RCTs would be valuable to increase transparency and attention to patient and public involvement.

AUTHOR CONTRIBUTIONS

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Formal analysis: Anders Granholm.

Funding acquisition: Morten Hylander Møller, Anders Perner, Anders Granholm.

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Third author involved in resolving discrepancies: Emily Barot, Anders Granholm.

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CONFLICT OF INTEREST

The Department of Anaesthesiology at Zealand University Hospital Køge has received funding for other projects from the Novo Nordisk Foundation and conducts research for AM-Pharma.

The Department of Intensive Care at Rigshospitalet–Copenhagen University Hospital has received funding for other projects from The Novo Nordisk Foundation, Pfizer, Fresenius Kabi, and the Lundbeck Foundation, and conducts contract research for AM-Pharma.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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