

Sample size estimation in clinical trials using ventilator-free days as the primary outcome: a systematic review

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SAMPLE SIZE ESTIMATION IN CLINICAL TRIALS USING VENTILATOR-FREE DAYS AS THE PRIMARY OUTCOME: A SYSTEMATIC REVIEW.

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18 ABSTRACT

19 Background

- 20 Ventilator-free days (VFDs) are a composite endpoint increasingly used as the primary
- 21 outcome in critical care trials. However, because of the skewed distribution and competitive
- 22 risk between components, sample size estimation remains challenging. This systematic
- 23 review was conducted to systematically assess whether the sample size was congruent, as
- 24 calculated to evaluate VFDs in trials, with VFDs' distribution and the impact of alternative
- 25 methods on sample size estimation.

26 Methods

- 27 A systematic literature search was conducted within the Pubmed and Embase databases for
- randomized clinical trials in adults with VFDs as the primary outcome until December 2021.
- 29 We focused on peer-reviewed journals with 2021 impact factors greater than five. After

30 reviewing definitions of VFDs, we extracted the sample size and methods used for its

31 estimation. The data were collected by two independent investigators and recorded in a

32 standardized, pilot-tested forms tool. Sample sizes were calculated using alternative

33 statistical approaches, and risks of bias were assessed with the Cochrane risk-of-bias tool.

34 Results

35 Of the 26 clinical trials included, 19 (73%) raised "some concerns" when assessing risks of 36 bias. Twenty-four (92%) trials were two-arm superiority trials, and 23 (89%) were conducted 37 at multiple sites. Almost all the trials (96%) were unable to consider the unique distribution 38 of VFDs and death as a competitive risk. Moreover, significant heterogeneity was found in 39 the definitions of VFDs, especially regarding varying start time and type of respiratory 40 support. Methods for sample size estimation were also heterogeneous and simple models, 41 such as the Mann–Whitney–Wilcoxon rank-sum test, were used in 14 (54%) trials. Finally, 42 the sample sizes calculated varied by a factor of 1.6 to 17.4.

43 **Conclusions**

A standardized definition and methodology for VFDs, including the use of a core outcome
set, seems to be required. Indeed, this could facilitate the interpretation of findings in
clinical trials, as well as their construction, especially the sample size estimation which is a
trade-off between cost, ethics, and statistical power.

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- 49 2021. (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021282304)
- 50 **Keywords**: respiration, artificial · respiratory insufficiency · time factors · treatment outcome
- 51 · ventilators, mechanical.

52 **BACKGROUND**

53 Between a quarter and half of the patients admitted to the intensive care unit will 54 present with respiratory failure, requiring invasive mechanical ventilation[1]. These patients 55 are at risk of complications, such as ventilator-associated pneumonia and death, with related 56 health-care costs[2,3].

57 Mortality is a robust endpoint that has long been used in studies[4]. However, since 58 the improvement of therapeutics, mortality has decreased[5], and the sample size needed to 59 show a clinically relevant difference in mortality has also increased. Hence, most published 60 randomized clinical trials (RCTs) that aim to reduce mortality have produced negative 61 results[6,7]. For this reason, other outcomes have been developed, such as ventilator-free 62 days (VFDs), which are increasingly used in critical care RCTs[8]. First proposed in 1994[9], 63 VFDs were developed in studies focusing on acute respiratory distress syndrome. The 64 number of VFDs was defined as the number of days from the last day of mechanical 65 ventilation to day 28. If a patient died during the first 28 days, their number of VFDs is equal to zero. This composite outcome measure (i.e., combining survival and the duration of 66 67 ventilation) is more appropriate than only the duration of ventilation because the latter 68 disregards the mortality rate[10].

In clinical research, it is not feasible, for most studies, to study the whole population[11]. We therefore need to determine the sample size, which can be imprecise and difficult. Indeed, it represents a trade-off between cost effectiveness (i.e., in terms of time and resource), ethical concerns (e.g., an oversized experiment would result in exposure of an unnecessary number of subjects) and statistical power (i.e., a small sample size could make the study underpowered to show a clinically meaningful difference, if any, and to

75	detect a potentially effective treatment)[12]. Calculating this sample size involves the
76	employment of formulae designed to obtain significant results in studies that compare
77	several groups based on the primary endpoint. The test chosen to analyze the primary
78	endpoint will depend on its distribution and is part of the sample size estimation[13]. VFDs
79	do not follow a Gaussian distribution[14]; therefore, we cannot use parametric tests. Indeed,
80	the distribution is skewed with inflations, especially 0s, and represents a rather time-
81	dependent event. In their last review, Yehya et al.[8] recommended using competing risk
82	regression, such as the Fine and Gray competing risk regression[15], which considers
83	extubation success as the event of interest and death as the competing risk.
84	There appears to be a number of inconsistencies in the definitions and
85	methodologies used for VFDs in the literature[8,16]. As a result, we conducted a systematic
86	review of RCTs using VEDs as the primary outcome to evaluate them. Hence, our principal
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87	objective was to investigate whether the sample size estimation of VFDs was congruent with
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87 88 89 90 91	objective was to investigate whether the sample size estimation of VFDs was congruent with their true distribution. Indeed, incorrect sample size estimation may lead to additional costs, expose an unnecessary number of subjects or decrease the power of a study. Our secondary objectives were to review the definitions of VFDs and to evaluate different statistical approaches to their estimation.

92 Methods

93 Search strategy, study selection and inclusion criteria

We searched through two databases (MEDLINE and Embase) using a combination of
keywords. The last literature search was done on December 31, 2021. We only focused on
RCTs with VFDs as the primary outcome in peer-reviewed journals with 2021 impact factors
greater than five. The complete list of search terms is available in the online data

98 supplement (Additional file 1: Appendix 1). Two investigators (LRT and MJ) independently 99 screened the titles and abstracts of the search results. The full text of all potentially eligible 100 studies was retrieved and reviewed for eligibility. First, we removed the duplicates between 101 the databases. Then, we excluded all trials that were not RCTs in adults and those with the 102 primary endpoint that was not VFDs. A narrative synthesis supporting the Preferred 103 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and the 104 PRISMA 2020 Checklist[17] were included as part of this systematic review. The study 105 protocol was registered with the International Prospective Register of Systematic Reviews 106 (PROSPERO) in December 2021 (ID: CRD42021282304)[18].

107 Data extraction

Data were extracted independently by two investigators (LRT and MJ or BP) and collected into standardized forms using Research Electronic Data Capture tools[19,20]. Data were cross-checked; any disagreements were resolved first by consensus, and if one or several disagreements persisted, a third investigator (BP or MJ) was involved. For each selected article, we recorded several items, as detailed in the online data supplement (Additional file 1: Appendix 2).

114 **Risk of bias**

To assess the risk of bias in each study, we used Version 2 of the Cochrane risk-ofbias tool (RoB2) for RCTs[21]. The studies were assessed using five fixed domains, as outlined in RoB2. Each study was classified by two investigators (LRT and MJ) as having "low risk," % some concerns," or "high risk."

119 Outcomes

Our primary outcome was the sample size, as estimated in RCTs evaluating VFDs as their primary outcome. First, we extracted the sample sizes estimated and observed among the trials. Secondly, because there is heterogeneity in the tests used for this outcome, we simulated other sample sizes through alternative statistical approaches. Our secondary outcomes were to review the definitions of VFDs, mortality rates, statistical methods, and VFDs' distributions among selected trials.

126 Statistical analysis

127 The different statistical approaches were as follows: the Student *t*-test and the 128 Mann–Whitney–Wilcoxon rank-sum test because these are standard tests used in several 129 studies; the Mann–Whitney–Wilcoxon rank-sum test using the Noether formula to compare 130 if the result differ from the previous one; the Cox regression because VFDs are considered by 131 some to be a time-dependent event; the zero-inflated negative binomial regression because 132 VFDs involve a zero-inflation; and finally, the Fine and Gray regression because the VFDs 133 involve death as a competitive risk. The corresponding formulae are available in the online 134 data supplement (Additional file 1: Appendix 3). All statistical analyses were performed using 135 R Core Version 4.2[22]. All packages used are listed in the online data supplement 136 (Additional file 1: Appendix 4).

137 **Results**

138 **Study selection and characteristics**

We identified 425 studies from 2004 to 2021. After removing duplicates, we assessed 269 studies. One hundred and thirty-six non-randomized studies were excluded, as well as two animal studies and 29 pediatric studies. We then excluded 76 studies in which the primary outcome was not VFDs. Twenty-six studies were finally included in our systematic

review[23–48] (Additional file 1: Figure S1). These were 24 (92%) superiority studies
comparing two groups (three for the two remaining) among several centers (median [IQR],
23 [8–42]) for 22 (85%) trials. An interim analysis was performed in 16 (58%) trials. Ten (39%)
of the selected studies had to be stopped early. Finally, the patient populations included in
these studies were heterogeneous, with a third having acute respiratory distress syndrome
(see Table 1 and Additional file 1: Table S1).

149 **Risk of bias and disagreements**

Using the Excel spreadsheet provided by the RoB2 tool, we assessed the risk of bias, as summarized in Table S2. Nineteen (73%) of the studies were assessed as having "some concerns," mainly related to the randomization process and deviations from the intended interventions.

Among all the collected items, the median [IQR] number of disagreements between the two reviewers was 1 [0 – 2] out of the 26 selected studies, for a total of 23 disagreements out of 769 items (3%). All disagreements were resolved by consensus.

157 Sample size estimation

We extracted the estimated and observed sample sizes reported in the selected studies. We subsequently estimated the sample size with parameters (e.g., risk, power, mean difference) reported in two ways: using the expected parameters displayed in the Material and Methods section or the observed parameters displayed in the Results section. First, we reported the expected parameters proposed by the authors for the sample

163 size estimation in the Methods sections of the selected studies (see Table 2 and Additional

164 file 1: Table S3). The absolute mean difference in VFDs ranged from 0.5 to 7.0. In one

165 noninferiority study[30], the authors considered 1.6 to be the noninferiority margin, 166 whereas in one superiority study[29], the authors considered 1 to be the superiority margin. 167 These expected mean differences were only justified in eight (31%) studies. The standard 168 deviation was only reported in 23% of studies, but, when it was available, it was 169 heterogenous (median [IQR], 10.0 [6.8 – 10.5]) (Figure S2). Mortality was considered in one 170 study only[26], in which Markov chains considered the probabilities of death, getting off 171 ventilation alive, and receiving ventilation. Finally, the expected dropout rate was quite 172 diverse among studies (0% - 25%).

173 Using these parameters (i.e., mainly mean difference and standard deviation), we 174 calculated, as reported in Table S4, the different sample sizes resulting from different 175 statistical tests: the Student *t*-test, the Mann–Whitney–Wilcoxon rank-sum test using the 176 Noether formula or not, the Cox regression, the zero-inflated negative binomial (ZINB) 177 regression, and the Fine and Gray regression. Several models could not be computed 178 because of some expected parameters not being reported, such as the VFDs in the control 179 group and their standard deviation. Moreover, it was not possible to estimate the sample 180 size using the Fine and Gray regression because neither the probability of extubation nor the 181 mortality incidence was reported. For estimations using Cox and ZINB regression, in most 182 cases, the sample size was greater than with other models and slightly higher with Cox 183 regression than with ZINB regression (see Figure 1). The median [IQR] of the maximum 184 variation factor between sample size estimations was 1.9 [1.7 - 3.5], with a maximum of 185 17.4.

186 Second, we reported the observed parameters needed to estimate the sample size187 (Additional file 1: Table S5). Standard deviations were slightly different from those estimated

(absolute median difference [IQR], 4.5 [1.0 – 6.9]). Furthermore, the dropout rate observed
was very low (0% – 2%).

190 Using these parameters, we calculated the different sample sizes using the same 191 statistical tests as above (Additional file 1: Table S6). Sample sizes could not be estimated using the Fine and Gray regression model because, for some studies, VFDs and the mortality 192 193 incidence had different timeframes. In addition, the incidence of extubation was never 194 reported in the selected studies. We did not estimate the sample sizes in about half of the 195 studies because the observed mean difference was too low (i.e., when the mean difference 196 was less than 1). Indeed, conducting a study with such an effect size would appear irrelevant 197 and clinically unrealistic.

Finally, because several data useful to estimate the sample size, especially for the Fine and Gray regression, were not reported, simulation was carried out from a previously published dataset by Bodet-Contentin et al.[49]. We estimated the sample size using this simulation and the same tests as above (Additional file 1: Table S7). Only the estimation using the Fine and Gray regression model provided a realistic sample size. However, this was more of a thought experiment because the effect size was low (mean difference = 0.46) and further simulation studies are warranted.

205 **Definitions of ventilator-free days**

The definitions of VFDs across selected studies are reported in Table 3. Almost all studies counted whole days without support ventilation (92%) and calculated VFDs at day 28 after randomization. Other definitions were heterogeneous. The onset (i.e., the beginning of the period without support ventilation) was not the same across studies: 35% considered the onset at extubation and 38% at 48 hours after extubation. If a patient was intubated again

after a period of extubation, the count of VFDs started only after the last extubation event in 35% of the studies, and 27% of the studies summed the different periods during which the patient was extubated; the remaining studies did not specify this point. Finally, half of the studies did not mention the type of respiratory support (invasive or noninvasive) used to define VFDs.

216 <u>Statistical methods to analyze ventilator-free days: distribution and statistical tests used</u>

217 The proper sample size estimation necessitates a correct estimation of the 218 distribution of VFDs. Distributions of VFDs, as defined by the authors of the selected studies 219 are reported in Table 2 and Table S3. Half of the studies did not explicitly state the type of 220 assumed distribution, whereas the other half did not consider VFDs to be normally 221 distributed. A more precise description was available for some studies, with 8% assuming a 222 zero-inflated binomial distribution and 4% assuming a bimodal distribution. However, two 223 recently published studies[32,35] considered the number of VFDs to be normally distributed. 224 We therefore simulated a normal distribution of VFDs with the parameters used in some 225 trials included in our systematic review, which was not consistent with the empirical 226 distribution of VFDs found in Jabaudon et al.'s meta-analysis[50] (see Figure 2).

We also reported the statistical analysis methods used to assess VFDs in the selected studies (see Table 2 and Additional file 1: Table S3). About one-third used the Mann– Whitney–Wilcoxon rank-sum test, one-fifth did not specify the test used, and more than a third used parametric tests. A minority used complex models, such as generalized linear mixed models (GLMM) and generalized additive models for location, scale, and shape (GAMLSS). The main effect size reported was the absolute mean difference (in 69% of studies) (Additional file 1: Table S4). A significant result for VFDs was obtained only in a few

studies (35%), but it was significant when a complex model was used (Additional file 1: TableS6).

236 Other characteristics

237 The power ranged from 80% (for 73% of the studies) to 90%, and the α risk ranged

from 2.5% to 10% (for one study[37]); however, the α risk was most frequently 5% (see

Table 2 and Additional file 1: Table S3). The reported α risk was one-sided in four studies

240 (two were noninferiority studies[30,33] and two were superiority studies[35,37]).

241 The most used timeframe for mortality was 28 days (Additional file 1: Table S5),

corresponding to the same frame as for VFDs. The timeframe was reported in days in 92% of

243 the studies; the remaining two used hospital or intensive care unit mortality. The incidence

of death was quite different across the studies but similar within studies, with a median

245 [IQR] of 24.9 days [19.2–30.9] for the control group and 24.3 days [19.8–30.7] for the

246 experimental group.

Finally, only three (12%) trials planned multiple imputation for the missing values
management, whereas the others did not plan any.

249 **Discussion**

In this systematic review, sample size estimation for assessment of VFDs in critical care trials was heterogeneous and not in adequacy with the actual distribution of VFDs. There was also important heterogeneity in the definitions of VFDs and in the methods used for sample size estimation among trials. Sample size estimation extends beyond the VFDs to all medical fields. Indeed, it is essential to have the right estimate before beginning a trial because of several aspects, such as ethical, logistic, and financial concerns. When there is

heterogeneity of both outcome definition and methods for calculating it, the sample size
may be underestimated and lack the power to show a clinically meaningful difference, or it
may be overestimated and waste resources and expose an unnecessary number of subjects
to a potentially harmful treatment, or deny a potentially beneficial one[11–13].

260 Sample size estimation: consensus definition of the outcome

Following Contentin et al.[16] and Yehya et al.[8], we found important differences between definitions of VFDs across trials, thus making it difficult to conduct meta-analyses, as there is no common core.

264 Yehya et al. made several recommendations, including on how to explicitly define 265 VFDs[8]. Hence, a core outcome set, such as the Core Outcomes in Ventilation Trials[51], 266 could be used. This includes standardized definitions and measures for extubation, 267 reintubation, duration of mechanical ventilation, and mortality. However, although 268 Blackwood et al. defined several components of VFDs, there was no consensual definition of 269 VFDs. In future studies, all components of this outcome should be reported to facilitate the 270 preparation of the future statistical analysis plan, especially for the sample size estimation 271 because it includes some of these components.

Finally, other alternative approaches should be considered such as a ranked composite score used in The Esophageal Pressure-Guided Ventilation 2 trial (EPVent-2)[52]. Alive and ventilator-free (AVF), the primary outcome used in EPVent-2, is a recent hierarchical composite outcome that does not treat mortality as equivalent to prolonged intubation[7]. This kind of outcome is already applied to other disciplines than critical care, such as in lung and cardiovascular clinical trials[53,54]. In a simulation-based study[7], AVF had higher power to detect differences in mortality than VFDs. Consequently, the sample

size could be lower with this outcome when there is a difference in mortality. Moreover, this
outcome typically requires fewer patients because its distribution is closer to a Gaussian
distribution than the distribution of VFDs. Finally, unlike AVF, which takes clinical priorities
into account, VFDs treat death or remaining intubated in the same way (i.e., if they were of
equal relevance). In contrast, death is considered more important than the duration of
mechanical ventilation in AVF, which seems more clinically relevant.

285 Sample size estimation: methods

286 Several parameters are required to estimate the sample size of an RCT. First is the tail 287 of the risk (one- or two-sided). In most superiority studies from our review, the authors used 288 a two-tailed test. However, if a specific and unidirectional difference is hypothesized (e.g., 289 treatment *vs* placebo), a one-sided risk should be preferred to test the null hypothesis for 290 the two groups[55].

291 We also need the expected difference (i.e., the effect size) between two groups in a 292 superiority study or a loss of efficacy in a noninferiority study. Some studies from our review 293 used a superiority margin smaller than the noninferiority margin, which is hardly justifiable. 294 Furthermore, VFDs do not follow a Gaussian distribution and using the median difference as 295 the effect size when estimating sample size seems more relevant than using the mean 296 difference. In addition, the expected standard deviation was heterogeneous across studies. 297 Even if the population was different, the standard deviation should not have such a large 298 difference for the same outcome. A consensus according to the context to choose the 299 correct effect size and the related standard deviation seems to be necessary to estimate the 300 right sample size and ensure sufficient powered.

301 Finally, 73% of the included studies had chosen a power of 80% for sample size 302 estimation. Therefore, if the other parameters for this estimation are under- or 303 overestimated, there is limited room for mistake.

304 Sample size estimation: statistical methods for ventilator-free days

There are two concepts to consider when using VFDs: their distribution and the presence of competitive risks. However, there are rarely reported, which may contribute to the fact that most included trials were underpowered.

308 First, the unique distribution of VFDs could make their statistical analysis more 309 problematic. Indeed, some articles reported a zero-inflated beta distribution[30,31]. For this 310 distribution, a GLMM[31,43] (e.g., with a zero-inflated beta model or hurdle-negative 311 binomial model[56]) or a GAMLSS[30] can be used. These models also allow for adjusting 312 covariates, thus reducing the sample size and increasing the power[57]. Here, VFDs are 313 treated as a count outcome, where death, intubation, and extubation are treated together 314 and combined as one entity. These models assess whether there is a difference between 315 groups on distribution. However, there was important heterogeneity in the reported 316 distribution of VFDs and in the tests used among trials, which prompts further clarification.

Second, regarding the presence of competitive risks, Yehya et al.[8] recommended reporting the mortality because the number of VFDs combines mortality and the duration of ventilation. Because mortality is a competitive event of extubation, competing risk regression using the Fine and Gray regression or the Cox-specific regression seem more appropriate than the usual tests, such as the Student *t*-test or Mann–Whitney–Wilcoxon rank-sum test[15]. In addition, not taking mortality into account may underpower the study, especially if mortality is low. Moreover, these tests enable adjustment for covariates and

interim monitoring, which are common in RCTs. Nevertheless, the cumulative incidence
function provided by the Fine and Gray regression does not have a natural interpretation[58]
and does not take the zero inflation into account. Here, VFDs are treated as a time-to-event
outcome. However, in our opinion, this does not express the real definition of VFDs. Indeed,
it is more the extubation time that is shaped, with death as a competitive risk.

As a result, these two types of models are based on two distinct concepts: a count outcome or a time-to-event outcome, not comparing the same things. Indeed, as mentioned above, the different parts of the VFDs components (i.e., death and ventilation duration) have a different importance depending on the type of model used, which is not much discussed in the literature. However, a recent study looked into the count outcome[59]. No model was globally recommended, the best model depends above all on the expected data distribution. However, to date, there is no clear answer as to which statistical test to use.

336 Nevertheless, based on the current results, we believe the usual tests should be 337 discouraged for analysis of VFDs and more complex models considering competitive risks, 338 the unique distribution of VFDs, and any covariates, such as centers, might be more 339 appropriate for better fit the data.

340 Sample size estimation: recent methodological approaches

341 Common formulae can be used to estimate a trial's sample size[13]. However, for 342 complex models such as the GLMM and GAMLSS, these formulae cannot be employed, and 343 simulation-based power analyses could be useful[60].

344 The Markov chain model is another interesting approach to stochastically describe a 345 sequence of possible events in which the probability of each event depends only on the state

346 attained by the previous event[61]. In the case of VFDs, three possible states could be 347 defined: intubated, extubated, or dead.

348 The use of simulations to estimate the sample size should probably be encouraged, 349 especially for VFDs, given their complex probability distribution[8].

350 **Limitations**

351 We only selected studies involving adults to focus on one type of population and 352 reduce population heterogeneity. Therefore, only RCTs were included because these studies 353 must report sample size estimation and are less prone to bias. Moreover, because we knew 354 there was heterogeneity in how VFDs are defined, we selected studies published only in 355 journals with a 2021 impact factor greater than five in the hopes of a more rigorous 356

methodology. However, in this systematic review we found few unbiased studies.

The selected studies included different populations, mainly because the inclusion

358 criteria of the reported studies were quite different, thus reducing the possibility of 359 generalizing our results. However, we focused on sample size estimation, which was not 360 affected by differences between studies. Moreover, some data of interest were not reported 361 in many studies, which restrained sample size estimation. Additionally, Harhay et al.[6] 362 found that 63% of the power parameters were unreported in selected RCTs.

363 **Strengths**

357

364 To our knowledge, this is the first systematic review of 26 RCTs assessing how sample 365 sizes are estimated in trials with VFDs as the primary outcome. First, we followed the 366 PRISMA 2020 statement guidelines with checklists[17] (Additional file 1: Tables S8 and S9). 367 Second, two investigators independently reviewed the studies. Third, we used two

databases to be as comprehensive as possible. In addition, we did not place any limit on the
publication year: All studies referenced since the creation of the database were therefore
included but restricted to journals with an impact factor greater than five. Finally, we used
the RoB2 tool to evaluate any potential biases.

372 **Conclusions**

373 In this systematic review of RCTs with VFDs as the primary outcome, we observed 374 strong variability in the methods and results of sample size estimation, in addition to 375 heterogeneity in the definitions of VFDs. Moreover, the uncommon distribution of the 376 number of VFDs in clinical trials may have important implications which warrants further 377 investigation, such as for sample size estimation and analysis. Complex models and 378 simulation might be useful for sample size estimation when using VFDs as a primary 379 outcome in future trials. The methods used are of great importance as they directly impact 380 the number of patients to enroll and could jeopardize the feasibility of a trial, due to ethical, 381 logistical, and financial reasons.

382 **ABBREVIATIONS**

- 383 EPVent-2: The Esophageal Pressure-Guided Ventilation 2 trial
- 384 GAMLSS: generalized additive model for location, scale, and shape
- 385 GLMM: generalized linear mixed model
- 386 IQR: interquartile range
- 387 PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- 388 RCTs: randomized clinical trials
- 389 RoB2: Version 2 of the Cochrane risk-of-bias tool
- 390 VFDs: ventilator-free days

391 ZINB: zero-inflated negative binomial

392 **DECLARATIONS**

393 <u>Ethics approval and consent to participate:</u> not applicable.

394 <u>Consent for publication:</u> not applicable.

- 395 Availability of data and materials: the datasets used and/or analysed during the current
- 396 study are available from the corresponding author on reasonable request. An annotated R
- 397 code for sample size simulations is available in open access in Zenodo[62].
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- 407 Formal analysis, Investigation, Writing Original Draft, Visualization; EF: Validation, Writing
- 408 Review & Editing, Supervision; MDC: Investigation, Resources, Writing Review & Editing;
- 409 NPD: Investigation, Resources, Writing Review & Editing; LBC: Resources, Writing Review
- 410 & Editing; MJ: Conceptualization, Methodology, Validation, Writing Review & Editing,

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607 **FIGURES**

608 Figure 1. Sample size estimation as reported in each trial and computed according to

609 different alternative tests.



610 For each study, sample size estimation is plotted (in blue) against the highest value among the sample size estimated in the study and five

611 different tests: the **Student** *t*-test, the Mann–Whitney–**Wilcoxon** rank-sum test, the Mann–Whitney–Wilcoxon rank-sum test using the

612 Noether formula, Cox regression and zero-inflated negative binomial (ZINB) regression. When an estimation is missing, the whole length of

- 613 the line is gray. The estimation was only possible for the following studies: Mackle[25]; Villar[26]; Zhou[27]; Trouillet[28]; Simonis[29];
- 614 Algera[30]; Tomazini[31]; Grieco[32]; Spragg[34]; Welte[35]; Rice_1[36]; Chung[38]; Rice_2[39]; Bein[40]; Kacmarek[42]; Liu[44];
- 615 Rice_3[45]; Matthay[46]; Bennett[47]; and McAuley[48].



616 Figure 2. Distribution of ventilator-free days (VFDs) in selected trials.



618 estimation and (b) the empirical distribution of VFDs (mean of 11.7 days, standard deviation of 10.71 and median of 12.23, interquartile

620 distribution were normal.

⁶¹⁹ range 0.00–22.00) found in Jabaudon et al.'s meta-analysis.[50] The red bars correspond to the theoretical data that should be seen if the

621 **TABLES**

Variable	n/N (%) or median [IQR]
Year of publication	
	2014 [2011 – 2020]
Journal	
AIM	1/26 (4)
AJRCCM	4/26 (15)
CCM	6/26 (23)
ICM	4/26 (15)
JAMA	7/26 (27)
LRM	1/26 (4)
NEJM	3/26 (12)
Number of group – ratio (E/C)*	
2 – 1:1	23/26 (88)
2 – 4:1	1/26 (4)
3 - 1:1:1	2/26 (8)
Study type	
Superiority	24/26 (92)
noninferiority	2/26 (8)
Number of center if multicentric ⁺	23 [8 – 42]
Interim analysis	16/26 (62)
Stopped earlier than expected	10/26 (39)
Population	
ARDS or ALI	14/26 (54)
COVID-19	3/26 (12)
Overall RoB2 [‡]	
low risk	3/26 (12)
some concerns	19/26 (73)
high risk	4/26 (15)

622 **Table 1. Characteristics of the included studies.**

624 respiratory distress syndrome, CCM Critical Care Medicine, ICM Intensive Care Medicine, IQR interquartile range, JAMA Journal of the

625 American Medical Association, *LRM* The Lancet Respiratory Medicine, *n* number of study, *N* total number of studies, *NEJM* The New

626 England Journal of Medicine.

627 *The allocation ratio (E for experimental group and C for control group).

628 [†]There were 22 (85%) studies with more than one center.

629 *The overall risk-of-bias via RoB2 (Revised Cochrane risk-of bias tools for randomized trials)[21].

⁶²³ AIM Annals of internal medicine, AJRCCM American Journal of Respiratory and Critical Care Medicine, ALI acute lung injury, ARDS acute

Variable	n/N (%) or median [IQR]	NA (%)
Expected VFDs		
control group	14.00 [11.90 – 16.70]	10 (38)
experimental group	16.25 [14.88 – 19.77]	10 (38)
mean difference	2.60 [2.00 – 7.00]	3 (12)
standard deviation	10.00 [6.75 – 10.53]	6 (23)
VFDs distribution		13 (50)
asymmetric	3/26 (11)	
bimodal	1/26 (4)	
normal	2/26 (8)	
not normal	5/26 (19)	
zero-inflated distribution	2/26 (8)	
Correction if distribution was not considered normal		15 (57)
+ 15%	3/26 (12)	
Markov chains	1/26 (4)	
median comparison	1/26 (4)	
no correction	2/26 (8)	
nonparametric test	4/26 (15)	
Statistical model		5 (19)
ANOVA	5/26 (19)	
Kruskal-Wallis	1/26 (4)	
Student <i>t</i> -test	2/26 (8)	
Mann–Whitney–Wilcoxon rank-sum test	8/26 (30)	
quantile regression	1/26 (4)	
Cox regression	1/26 (4)	
GAMLSS	1/26 (4)	
GLM	2/26 (8)	
risk	5 [5 – 5]	0 (0)
Power (%)	80 [80 – 80]	1 (4)
Two-tailed test	21 (81)	1 (4)
Dropout rate expected	3.00 [0.00 – 9.00]	0 (0)
Mortality considered for sample size estimation	1/26 (4)	0 (0)

630 Table 2. Parameters reported for the sample size estimation of ventilator-free days.

631 ANOVA analysis of variance, GAMLSS generalized additive model for location scale and shape, GLM generalized linear model, IQR

632 interquartile range, *n* number of study, *N* total number of studies, *NA* not available, *VFDs* ventilator-free days.

Variable	n/N (%)
Onset	
no onset reported	9/26 (35)
> 4h	1/26 (4)
> 24h	3/26 (11)
> 48h	10/26 (38)
> 72h	1/26 (4)
portion of day with no onset reported	2/26 (8)
Respiratory support	
invasive ventilation	13/26 (50)
tracheostomy	12/26 (46)
ECMO	2/26 (8)
NIV	6/26 (23)
HFNO	1/26 (4)
no detail reported	13/26 (50)
Reintubation	
possible	7/26 (27)
reset	9/26 (35)
no detail reported	10/26 (38)
Day when VFDs are defined	
28	24/26 (92)
30	1/26 (4)
60	1/26 (4)

633 Table 3. Definitions of ventilator-free days.

ECMO extracorporeal membrane oxygenation, HFNO high-flow nasal oxygen, n number of study, N total number of studies, NIV

noninvasive ventilation, onset time at which the patient is considered free of ventilation and start counting whole days except for two

studies that considered portion of day, VFDs ventilator-free days.