Economic Evaluation

The Social Economic Return of a Positive End-Expiratory Pressure–Based Lung Recruitment Clinical Trial Program in Patients With Acute Respiratory Distress Syndrome

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A B S T R A C T

Objectives: This study aimed to estimate the socioeconomic return from the value of lives saved by the protocol indicated by the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART). ART was conducted through a multicenter randomized trial at 120 intensive care units from 9 countries, enrolling adults with moderate to severe acute respiratory distress syndrome. It investigated whether lung recruitment associated with positive end-expiratory pressure titration according to the best respiratory system compliance decreases 28-day mortality of patients compared with a conventional low-positive end-expiratory pressure strategy.

Methods: The value of lives saved was estimated by considering whether the trial findings were implemented in the eligible patient populations for 1 year, and then the social economic return was computed by subtracting the clinical trial costs from the gross benefit. The return was computed by subtracting the ART costs from its gross benefit.

Results: The ART net benefit is approximately 152 million dollars if it is implemented in 50% of eligible patients in Brazil under the baseline assumptions. For every dollar spent in the clinical trial, a return of 114 dollars was achieved in Brazil alone. If the trial findings are implemented in all eligible patients, then the trial return would be 229.5 dollars for every dollar invested with a net benefit of 304 million dollars.

Conclusions: These findings highlight the substantial economic benefit of clinical trials on acute respiratory distress syndrome treatments for society. It also points out that the public return of clinical trials can be potentialized when the new trial findings are fully implemented on eligible patients.

Keywords: acute respiratory distress syndrome, low-positive end-expiratory pressure strategy, positive end-expiratory pressure titration, social economic return.

VALUE HEALTH REG ISSUES. 2023; 33:27–32

Introduction

Acute respiratory distress syndrome (ARDS) is one of the most challenging clinical conditions of critical care medicine.[1] The pneumonia associated with COVID-19 evolves to ARDS in the most severe cases. Consequently, ARDS is a major cause of the need for invasive mechanical ventilation and death in COVID-19.[2] Several clinical trials have assessed the effect of treatments to reduce mortality rates of patients with ARDS.[3] Nevertheless, no study has evaluated the socioeconomic return generated by clinical trial–based protocols on the treatment of patients with ARDS.

Previous studies estimate the socioeconomic return of clinical trials on public health. Johnston et al[4] investigate the effect of a US National Institutes of Health program of clinical trials on public health and costs. Health Economics Research Group,[5] Glover et al,[6] and Glover et al[7] estimate the returns to the United Kingdom of publicly funded cardiovascular, cancer, and musculoskeletal disease (MSD) research, respectively. Australian Clinical Trials Alliance (ACTA)[8] assesses the overall health and economic impact of investigator-initiated clinical trials conducted by clinical trials in Australia. Luce et al[9] estimate the return on US investment in health.

This study estimates the social economic return of the protocol indicated by the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART).[10] ART was a clinical trial conducted by the Brazilian Research in Intensive Care Network that investigated whether lung recruitment associated with positive end-expiratory pressure (PEEP) titration according to the best respiratory system compliance decreases the 28-day mortality of patients with moderate to severe ARDS compared with a conventional low PEEP strategy.

Methods

Methodology

This article identifies the social economic return of the clinical trial from the value of lives saved if the trial findings were implemented in the eligible patient populations for 1 year and then computes the return by subtracting the relevant clinical trial costs from the gross benefit.

Impact on individual patient health

The main finding of ART is the 28-day mortality rate of 55.3% in patients with moderate to severe ARDS treated with lung recruitment and titrated PEEP compared with 49.3% in patients treated with low PEEP. Furthermore, it also indicates that an individual ARDS patient's chance of surviving increases by 5.95% if all intensive care units (ICUs) had stopped using the recruitment maneuver procedure since the ART findings became public and started using only the low PEEP protocol.

Note that if no ICUs used to adopt lung recruitment maneuver and PEEP titration protocol in ARDS patients before the ART, then the potential impact of trial on individual's health will be null because the trial will not induce any change in clinical procedure of ARDS patients.

Individual's mortality-avoidance adjusted life value

The trial shows that an individual ARDS patient can increase the chance of surviving by 5.95% when treated with the appropriate protocol. Then, the life value of an individual in that health condition also increases by that amount.

This study estimates the value of life using the value of a statistical life (VSL) approach.[11,12] The VSL of an individual is determined by the present value of this individual's market productivity. Given that individual productivity is convertible in labor market income, the VSL of an individual corresponds to the present value of the stream of all future labor income.

Given that this article evaluates the economic return of ART, it only estimates the value of life of an individual with the same characteristics as those in the clinical trial, which is a 51-year-old individual.

The next step is to determine the monetary value of the return of the trial on an individual patient's health. It corresponds to the individual benefit of the trial's finding, which is defined hereafter as the individual's mortality-avoidance adjusted value of life.

Number of people potentially affected

To estimate the potential socioeconomic return of the trial for society, one needs to identify the number of people potentially affected.

The number of people potentially affected in a year is obtained by combining the incidence rate of ARDS and the population in Brazil.

Value of potential lives saved

The value of potential lives saved is the individual's mortality-avoidance adjusted value of life multiplied by the number of people potentially affected in a year if the trial findings are implemented in all eligible patients.

The value of potential lives saved and the effective value of lives saved would be the same. For this reason, this article computes 2 key measures of the gross benefits of the trial: the potential gross benefit and the effective gross benefit of the trial.

Net benefit and return

The economic return of the trial is computed as the net benefit of the trial. This is computed by subtracting the effective gross benefit from the clinical trial costs.

The benefit-cost ratio is obtained by dividing the net benefit by the clinical trial costs. The benefit-cost ratio measures the public return in dollars of the clinical trial findings for every dollar invested.

Data

This study uses the relevant data from Brazil, given that the trial was conducted with public funds provided by the Brazilian Ministry of Health. All the monetary benefits and costs in this study were computed in Brazilian reais and then converted to US dollars as of December 2019, which is the most recent period for which there is information for all the relevant data for this article.

To estimate the value of life of an individual with the same characteristics as the ones in the clinical trial, a 51-year-old individual, 3 pieces of information are needed: (1) life expectancy of a 51-year-old individual, (2) all expected future labor income of a 51-year-old individual from his 52nd year of life to his last expected year of life, and (3) a discount rate to compute the present value of the future labor income streams.

Information on the life expectancy of a 51-year-old individual in Brazil is 30 years.[13] For the expected future labor income of a 51-year-old individual, this study uses the annualized average monthly labor income of all individuals who are between 51 years old and 81 years old (which is the last expected year of life of an individual who is 51 years old).[14] For this, the values from December 2019 were used. As a discount rate, the Selic rate of December 2019 was used, which was 4.5% per year. The Selic rate is the basic interest rate defined by the Central Bank of Brazil. To convert the value of life in US dollars, the official average dollar-Brazilian real exchange rate of December 2019 was used, which was 4.12 Brazilian reais per dollar.

To compute the number of people potentially affected in a year, information on the incidence rate of ARDS and on the Brazilian population are needed. The incidence rate was obtained from Li et al,[15] who found that the 2008 incidence rate (per 100 000 person-years) of moderate and severe ARDS was 38.3. According to the Brazilian Institute of Geography and Statistics, the Brazilian population in 2019 was 210 147 125 habitants.

Results

First Elements

The estimated value of life of an individual with the same characteristics as the ones in the clinical trial is $127 696. If an individual has ARDS and is treated with a lung recruitment maneuver and PEEP titration protocol, then the patients have a 44.7% chance of surviving.[10] Therefore, this individual ARDS patient's expected value of life becomes $57 080. Equivalently, if an individual has ARDS and is treated with a conventional low PEEP protocol, they have a 50.7% chance of surviving. Hence, this individual ARDS patient's expected value of life becomes $64 678.

The individual's mortality-avoidance adjusted value of life corresponds to the difference between the expected value of life of an individual treated with the conventional low PEEP protocol and the expected value of life of an individual treated with the lung

Table 1. The potential gross benefit of the trial.

Pretrial fraction of high PEEP in ICUs (%)	Potential gross benefit (US dollars) Incidence rate (Li et al[15])
100	611 528 960
90	550 376 064
80	489 223 168
70	428 070 272
60	366 917 376
50*	305 764 480*
40	244 611 584
30	183 458 688
20	122 305 792
10	61 152 896
0.2[†]	1 327 018[†]
0	0

ICU indicates intensive care unit; PEEP, positive end-expiratory pressure.
*This is the baseline scenario.
[†]This the pretrial fraction of high PEEP in ICUs that makes the potencial gross benefit equals to the clinical trial costs.

recruitment maneuver and PEEP titration one. It corresponds to $7598.

As the number of people potentially affected in a year is equal to 80 486 individuals, the value of potential lives saved can be calculated. The value of potential lives saved is equal to 611 528 960 dollars per year.

Main Results

The first result presented in this subsection is the potential gross benefit of the trial. Table 1[15] shows that if the pretrial fraction of high PEEP in ICUs was 50%, then the potential gross benefit of the trial was approximately 305 million dollars. The pretrial

Table 2. The effective gross benefit of the trial.

Fraction of ICUs stopped using high PEEP protocol after the ART (%)	Effective gross benefit (US dollars) Incidence rate (Li et al[15])
100	305 764 480
90	275 188 032
80	244 611 584
70	214 035 136
60	183 458 688
50*	152 882 240*
40	122 305 792
30	91 729 344
20	61 152 896
10	30 576 448
0	0

ART indicates Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial; ICU, intensive care unit; PEEP, positive end-expiratory pressure.
*This is the baseline scenario.

Table 3. The net benefit of the trial.

Fraction of ICUs stopped using high PEEP protocol after the ART (%)	Net benefit (US dollars) Incidence rate (Li et al[15])
100	304 438 069
90	273 861 621
80	243 285 173
70	212 708 725
60	182 132 277
50*	151 555 829*
40	120 979 381
30	90 402 933
20	59 826 485
10	29 250 037
0.4[†]	0[†]
0	−1 326 411

ART indicates Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial; ICU, intensive care unit; PEEP, positive end-expiratory pressure.
*This is the baseline scenario.
[†]This the Fraction of ICUs stopped using high PEEP protocol after the ART that makes the Potencial gross benefit equals to the Clinical trial costs.

fraction of high PEEP in ICUs equal to 50% corresponds to the base case assumption of this study.

Table 2[15] shows that if the pretrial fraction of high PEEP in ICUs and fraction of ICUs that have stopped using the recruitment maneuver procedure since ART became public are both 50%, then the effective gross benefit of the trial is approximately 152 million dollars.

The clinical trial costs amount to 1 326 411 dollars. Hence, the net benefit of the trial under the assumptions of Table 2[15] is described in Table 3[15] below.

Based on the base case assumptions that the pretrial fraction of high PEEP in ICUs and fraction of ICUs that have stopped using the recruitment maneuver procedure since the ART findings became public are both 50%, then the net benefit of the trial is approximately 151 million dollars.

Note also that if no ICUs have stopped using the recruitment maneuver procedure since the ART findings became public, among the ones that used to adopt such a protocol in ARDS patients, then the effective gross benefit is 0 (Table 2[15]), and the net benefit is negative (Table 3[15]). In contrast, if the ART findings were implemented in all ICUs that previously used the lung recruitment maneuver and PEEP titration protocol, then the net benefit of the trial would be approximately 304 million dollars.

Table 3[15] also shows that the results of the ART findings need to be implemented in only 0.4% of ICUs that previously used the lung recruitment maneuver and PEEP titration protocol for benefits to exceed costs (under the base case assumption that the pretrial fraction of high PEEP in ICUs was 50%).

Finally, the benefit-cost ratio, which is the ratio between net benefit and the clinical trial costs, is computed. Table 4 shows the benefit-cost ratio of the trial for different pretrial fractions of high PEEP in ICUs and different fractions of ICUs that had stopped using high PEEP since the ART findings became public.

Table 4 shows that under the base case assumption (the pretrial fraction of high PEEP in ICUs and the fraction of ICUs that have stopped using the recruitment maneuver procedure since the ART findings became public are both 50%), the benefit-cost

Table 4. Benefit-cost ratio.

	Pre-trial fraction of high PEEP in ICUs (%)	0	20	40	50*	60	80	100
Pre-trial fraction of high PEEP in ICUs (%)	0	−1.0	−0.8	−0.6	−0.5*	−0.4	−0.2	0.0
	20	−1.0	17.4	35.9	45.1*	54.3	72.8	91.2
	40	−1.0	35.9	72.8	91.2*	109.6	146.5	183.4
	50[†]	−1.0[†]	45.1[†]	91.2[†]	114.3*,[†]	137.3[†]	183.4[†]	229.5[†]
	60	−1.0	54.3	109.6	137.3*	165.0	220.3	275.6
	80	−1.0	72.8	146.5	183.4*	220.3	294.1	367.8
	100	−1.0	91.2	183.4	229.5*	275.6	367.8	460.0

ART indicates Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial; ICU, intensive care unit; PEEP, positive end-expiratory pressure.
*This is the baseline scenario for the Fraction of ICUs stopped using high PEEP Protocols after the ART.
[†]This is the baseline scenario for the Pretrial fraction of high PEEP in ICUs.

ratio is approximately 114 dollars. This corresponds to a public return on the trial of 114 dollars for every dollar invested. Table 4 also shows that if the ART findings were implemented in all ICUs that previously used the lung recruitment maneuver and PEEP titration protocol, then the result would be a return of 229.5 dollars for every dollar invested.

Sensitivity Analysis

Sensitivity analyses are used to investigate what would happen to the results if the major assumptions used in calculations were to change. The following assumptions were tested through sensitivity analyses: a different estimated number of people potentially affected (moderate to severe ARDS incidence) in a year and different VSLs.

Different estimated numbers for people potentially affected in a year

A sensitivity analysis of the public return of the trial was conducted by using moderate and severe ARDS incidence rates obtained by Caser et al.[16] They found that the annual incidence rate (per 100 000 person-years) of moderate and severe ARDS was 6.3.

The results of the ART findings need to be implemented in only 2.6% of ICUs that previously used the lung recruitment maneuver and PEEP titration protocol for benefits to exceed costs (assuming that pretrial fraction of high PEEP in ICUs was 50%). It also shows that under the base case assumption, the benefit-cost ratio is approximately 18 dollars. That corresponds to a public return of the trial of 18 dollars for every dollar invested. This sensitivity analysis shows that the public return of the trial is still remarkably high even when considering a low incidence rate of moderate to severe ARDS.

Different VSLs

Table 5[17-25] presents these different studies and provides country-specific references of the VSL. Brito[17] estimated that the VSL is $173 128.13. Nevertheless, Ferrari et al[18] estimated that the VSL in Brazil is $119 687.02.

Based on the VSL reported by Ferrari et al[18], presents the net benefit and the benefit-cost ratio of the trial for different fraction of ICUs that have stopped using recruitment maneuver procedure since the ART's findings became public.

The results of the ART findings need to be implemented in only 0.5% of ICUs that previously used the lung recruitment maneuver and PEEP titration protocol for benefits to exceed costs. It also shows that if the pretrial fraction of high PEEP plus lung recruitment in ICUs and fraction of ICUs that have stopped using recruitment maneuver procedure since the ART findings became public are both 50%, then the benefit-cost ratio is approximately

$107. This shows that the public return of trial using Ferrari et al[18] VSL has the same magnitude as the public return obtained in a previous subsection (the base case assumption).

Discussion

Our results show that the net economic benefit of ART was 152 million dollars in 1 year, assuming a low PEEP strategy was used instead of lung recruitment and a high PEEP strategy in 50% of eligible patients. In addition, for every dollar spent to fund the clinical trial, a return of $114 was achieved in a year just in Brazil.

The net benefit of the trial would be approximately 304 million dollars if the ART findings were implemented in all ICUs that previously used the lung recruitment maneuver and PEEP titration protocol. This finding indicates that economic return can be maximized if the new findings of trials are fully implemented on eligible patients.

Using a similar method, previous studies have estimated the economic impact and the public return of clinical trials on public health. Johnston et al[4] examine the impact of a US National Institutes of Health program of clinical trials on treatment cost and public health. Based on 28 trials that costed 335 million dollars, they found that 21% of the trials had improved in health, and 14% had reduced treatment cost. In a 10-year window, their estimates show that the program of trials saved approximately 470 000 quality-adjusted life-years for 3.6 billion dollars in total cost. By quantifying the value of the quality-adjusted life-year as gross domestic product per capita, the 10-year estimated net benefit of the trial program was 15.2 billion dollars. This is equivalent to 1500 million dollars per year, which corresponds to 58 million dollars per year per trial.

This study differs from Johnston et al[4] in important dimensions. First, it shows that the net benefit of ART is 2.62 times larger than the average net benefit of the 26 trials in the US National Institutes of Health program in Johnston et al[4] (152 million dollars vs 58 million dollars). The difference between the net benefits of the 2 studies resulted from the following features: (1) a sizable health impact on individual ARDS patients of the ART's finding, (2) a relatively small cost of the ART compared with the ones analyzed in Johnston et al,[4] and (3) the fact that the 2 protocols in the ART (lung recruitment and titrated PEEP vs conventional low PEEP) have the same health costs whereas 88% of the trials in Johnston et al[4] increase healthcare costs. Finally, Johnston et al[4] do not compute the potential public return if the trials' findings are fully implemented on eligible patients, a return computed in this article. This estimation is important, because it reveals the societal gains of integrating clinical trial findings with frontline healthcare delivery.

Table 5. References of VSL.

Reference	Country	VSL (US dollars 2019)
Brito[17]	Brazil	172 128.13
Ferrari et al[18]	Brazil	119 687.02
Mahmud[19]	Bangladesh	4069.54
Bhattacharya et al[20]	India	191 668.42
Iragüen and Ortúzar[21]	Chile	225 409.33
Yang et al[22]	China	1 119 432.27
Krupnick et al[23]	Canada	1 276 320.62
Svensson[24]	Sweden	3 552 509.74
Hensher et al[25]	Australia	7 579 769.80

VSL, value of a statistical life.

Using a similar approach, Glover et al[7] compute the return in terms of net value of improved health outcomes from research expenses on MSD research publicly funded by the United Kingdom. They find a benefit-cost ratio equal to 1.07 for MSD research, which corresponds to a return of 7%. Based on a different approach, Health Economics Research Group[5] and Glover et al[6] rely on a top-down approach to estimate the internal rate of return from UK publicly funded medical research on cardiovascular diseases (CVDs) and on cancer research. They find a return of 9% and 10% from CVD and cancer research, respectively. A cost-benefit analysis shows a benefit-cost ratio of 1.09 (for CVD research) and 1.10 (for cancer research). These numbers indicate that the benefit-cost ratio of ART is substantially larger than the benefit-cost ratio of all United Kingdom publicly funding medical research projects.

ACTA[8] investigates the economic return of 25 high-impact clinical trials conducted in Australia. ACTA[8] shows that if these trials were implemented for 1 year in 65% of the eligible patient populations in Australia, then a return of $51.10 is achieved for every $1 granted in the National Health and Medical Research Council awarded to these analyzed trials. Furthermore, they show that the net benefit is positive if the analyzed trials are implemented in 11% of the eligible patients.

By analyzing the economic and health impacts of different maternal and perinatal healthcare, Pham et al[26] compared innovative interventions and standard practices. They find a potential cost saving of $26.3 million over 5 years if the findings of the 6 most efficient interventions are implemented in 10% of the eligible populations. If they are implemented in 100% of the eligible patients, then the potential cost savings can reach $262.8 million. A comparison between the results in Pham et al[26] and those in this article reinforces our findings that ART has high economic benefit and large cost-effectiveness.

A comparison between ACTA[8] findings and the results in this article reveals important information. First, it shows that the benefit-cost ratio of ART is 2.62 times larger than the benefit-cost ratio of the 25 selected trials in ACTA[8]; a return of 114:1 was found for ART versus 51.1:1 for ACTA. Second, ART needs to be implemented in a lower fraction of the eligible population (0.4%) than the trials in ACTA,[8] which is 11%. This finding reveals that ART has a higher economic benefit and is more cost-effective.

This article is also related to earlier studies that estimate healthcare's return. Luce et al[9] analyzed data on US investment in healthcare from 1980 to 2000. They find that the return per dollar invested in healthcare ranges from 1.55 to 1.94 dollars. These figures reveal that ART is substantially larger than investment in overall healthcare services (a return of 114 dollars for each dollar invested was estimated for ART).

This study has some limitations. First, it relies only on ART clinical trials to draw conclusions about the socioeconomic return of clinical trials on ARDS treatments for society. Nevertheless, there is a very important reason for evaluating ART: it is a study that proposes a protocol that is easy to implement in ICUs at a negligent cost and, more importantly, has a striking effect on ARDS patients' chances of survival. Second, the analysis focused on Brazil since the initial trial investment was funded by the Brazilian government. Although the findings might not be generalizable elsewhere, given that values of health vary widely across countries, the evaluation method proposed in this article is applicable to other countries that wish to evaluate the economic return of the ART clinical protocol recommendation. Furthermore, Brazil is a typical developing country where governments frequently face the dilemma between funding healthcare services or academic research on health. The results show that the economic return of health research is considerably high in a developing country, and it is higher than the return of healthcare if one takes the returns computed by Luce et al.[9] Note that, ideally, we should relate our findings to similar ones obtained by studies performed in other developing countries, presumably more comparable with Brazil. Nevertheless, to the best of our knowledge, there are no other studies in the literature that estimate the social economic return of protocols like ART's one in developing countries, neither compute the social return of other cardiopulmonary protocols in similar countries. If, at the first glass, the lack of a cross-country comparison sounds like a limitation of our study, it can also be interpreted as a strength of our work given that it can be used as a source of comparison for future studies on the topic in developing countries. Finally, the estimates of the value of life may vary with the methods used for assessment, producing uncertainty in the overall economic value of the ART. Nevertheless, the overall public return of the ART has a similar magnitude when considering other estimates for value of life.

Conclusions

Our findings highlight the substantial public economic return of funding clinical trials of treatments for critically ill patients in middle-income countries, such as Brazil. It also points to the potential of well-designed clinical trials to improve healthcare quality through cessation of ineffective interventions. The social economic return of clinical trials can be potentialized when the new trial findings are fully implemented on eligible patients, and efforts are made to integrate clinical trial findings with frontline healthcare delivery.

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