

# USE AND ORGANISATION OF ECMO IN BELGIUM

## SUPPLEMENT





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## COLOPHON

|                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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Reported interests:

'All experts and stakeholders consulted within this report were selected because of their involvement in the topic of <ECMO use in Belgium>. Therefore, by definition, each of them might have a certain degree of conflict of interest to the main topic of this report'

Membership of a stakeholder group on which the results of this report could have an impact: Philip Bastone (ESICM, ICS), Leen Vercaemst (EuroELSO)

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- The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.,
- Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content,
- Finally, this report has been approved by common assent by the Executive Board,
- Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.

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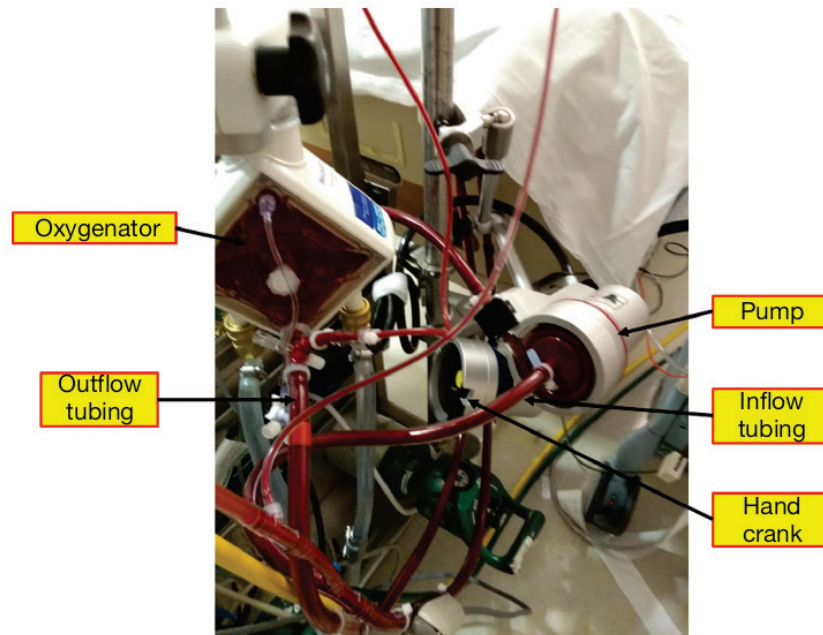


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## APPENDIX 1. INTRODUCTION AND SCOPE

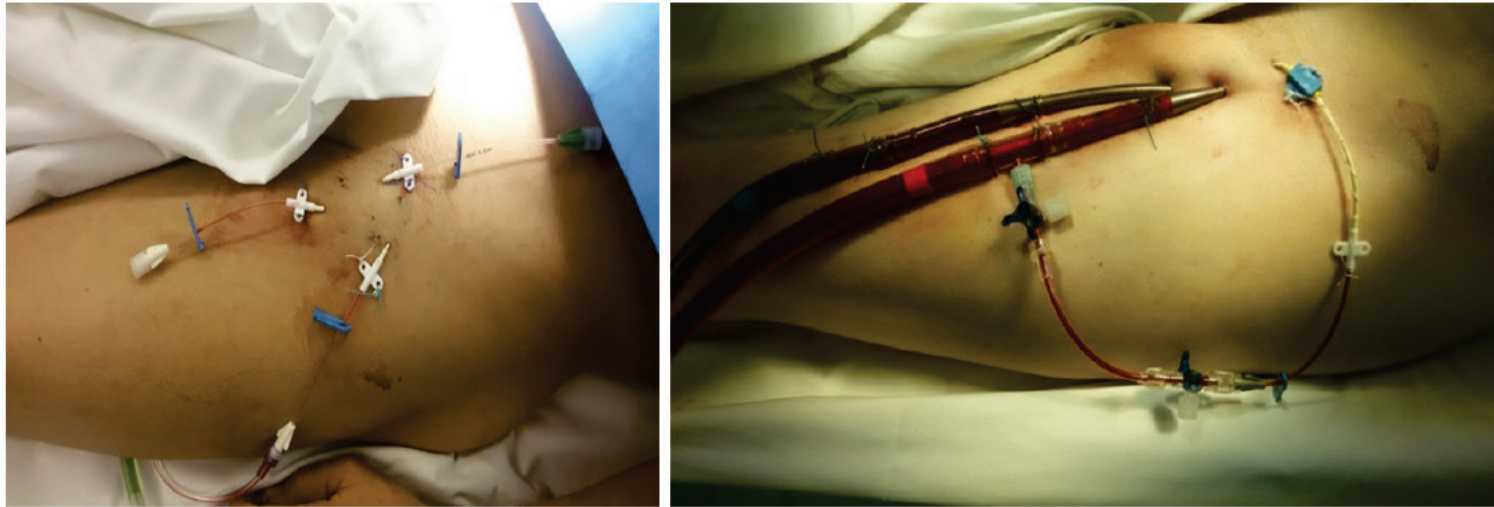
### Appendix 1.1. Components of the ECMO device



*Legend: ECMO cannula circuit and components (from Patel et al, 2019<sup>1</sup>)*



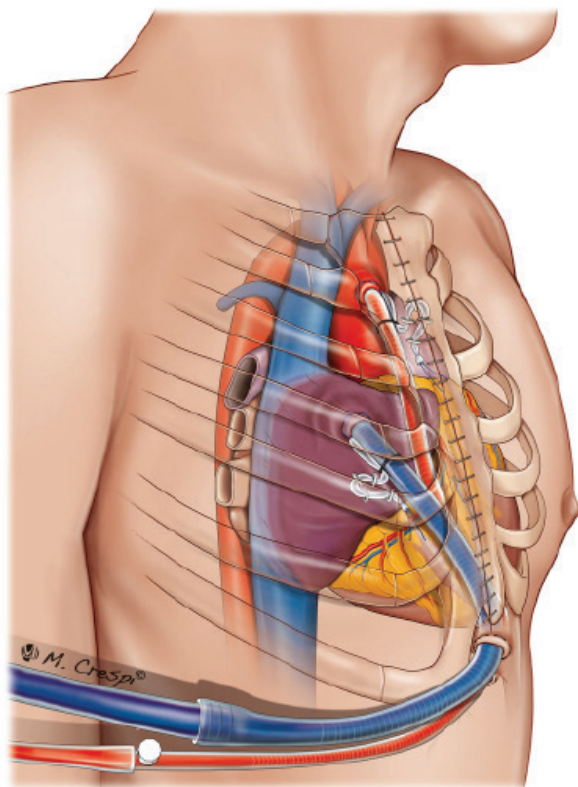
## Appendix 1.2. Percutaneous cannulation



*Legend : Percutaneous cannulation technique for VA-ECMO (from Poptvov et al – 2018<sup>2</sup>)*



### Appendix 1.3. Central cannulation



*Legend: central cannulation -right atrium and ascending aorta cannulation (from Lorusso et al-2019<sup>3</sup>)*



## APPENDIX 2. USE OF ECMO IN BELGIUM: PERIOD 2016-2019

### Appendix 2.1. Data selection

#### Appendix 2.1.1. Selection criteria: number of stays per year

| Analysis                                                                                | Selection criteria                                                                                                                                         | 2016 | 2017 | 2018 | 2019 | TOTAL       |
|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|------|------|-------------|
| Nb of stays, per hospital, per region, global patient demographics                      | Valid coupled stays(*)<br>with ECMO ICD-10-PCS code<br><b>OR</b> ECMO fee                                                                                  | 589  | 602  | 669  | 683  | <b>2543</b> |
| Adult demographics, qualification provider and survival analysis <b>by type of ECMO</b> | Valid coupled stays<br>with ECMO fee,<br>> 15 years                                                                                                        | 418  | 439  | 462  | 482  | <b>1801</b> |
| Adult clinical information                                                              | Valid coupled stays(*)<br>with ECMO ICD-10-PCS code,<br>> 15 years                                                                                         | 430  | 479  | 532  | 555  | <b>1996</b> |
| Adult clinical information <b>by type of ECMO</b>                                       | Valid coupled stays<br>with ECMO ICD-10-PCS code,<br><b>AND</b> ECMO fee,<br>> 15 years                                                                    | 305  | 361  | 388  | 405  | <b>1459</b> |
| Adult costs                                                                             | Valid coupled stays<br>with ECMO ICD-10-PCS code<br><b>AND</b> ECMO fee<br><b>AND</b> ECMO surveillance fee<br><b>AND</b> ECMO material fee,<br>> 15 years | 244  | 290  | 314  | 323  | <b>1171</b> |

(\*) Including stays with ICD-10-PCS code ECMO with no claim not covered by the national health insurance.



## Appendix 2.2. Demographics

### Appendix 2.2.1. Whole patient population (n=2543)

#### Stays with ECMO by patient type : adult vs paediatric

| Frequency<br>Col Pct | 2016         | 2017         | 2018         | 2019         | Total                       |
|----------------------|--------------|--------------|--------------|--------------|-----------------------------|
| Adult                | 543<br>92.2% | 557<br>92.5% | 606<br>90.6% | 632<br>92.5% | <b>2338</b><br><b>91.9%</b> |
| Paediatric           | 46<br>7.8%   | 45<br>7.5%   | 63<br>9.4%   | 51<br>7.5%   | <b>205</b><br><b>8.1%</b>   |
| <b>Total</b>         | <b>589</b>   | <b>602</b>   | <b>669</b>   | <b>683</b>   | <b>2543</b>                 |

#### Age of patients staying at hospital with an ECMO by year

| Age    | 2016 | 2017 | 2018 | 2019 | Total       |
|--------|------|------|------|------|-------------|
| N      | 589  | 602  | 669  | 683  | <b>2543</b> |
| Mean   | 51.6 | 51.3 | 51.4 | 53.6 | <b>52.0</b> |
| Std    | 20.9 | 20.5 | 21.0 | 20.5 | <b>20.8</b> |
| Median | 57   | 56   | 57   | 59   | <b>58</b>   |

**Stays of patients with ECMO by gender by year**

| Frequency<br>Col Pct | 2016         | 2017         | 2018         | 2019         | Total                       |
|----------------------|--------------|--------------|--------------|--------------|-----------------------------|
| Male                 | 378<br>64.2% | 392<br>65.1% | 446<br>66.7% | 465<br>68.1% | <b>1681</b><br><b>66.1%</b> |
| Female               | 211<br>35.8% | 210<br>34.9% | 223<br>33.3% | 218<br>31.9% | <b>862</b><br><b>33.9%</b>  |

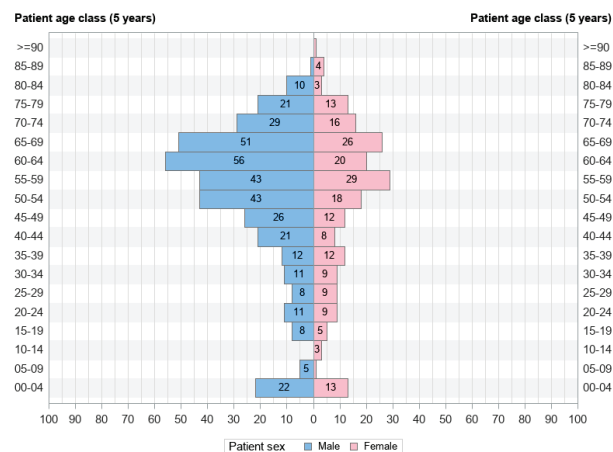
**Stays of patients with ECMO by gender and age**

| Age by sex | N    | Mean | Std  | Min | P10 | P25 | Median | P75 | P90 | Max |
|------------|------|------|------|-----|-----|-----|--------|-----|-----|-----|
| Male       | 1681 | 53.0 | 19.9 | 0   | 23  | 45  | 58     | 67  | 73  | 90  |
| Female     | 862  | 48.8 | 22.7 | 0   | 18  | 37  | 56     | 66  | 75  | 90  |

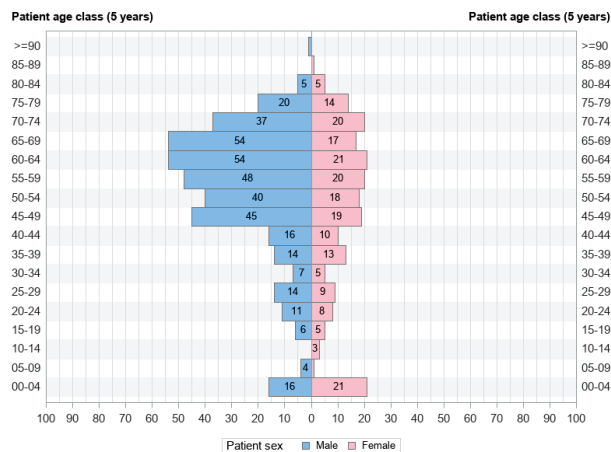


## ECMO patient population pyramid by year

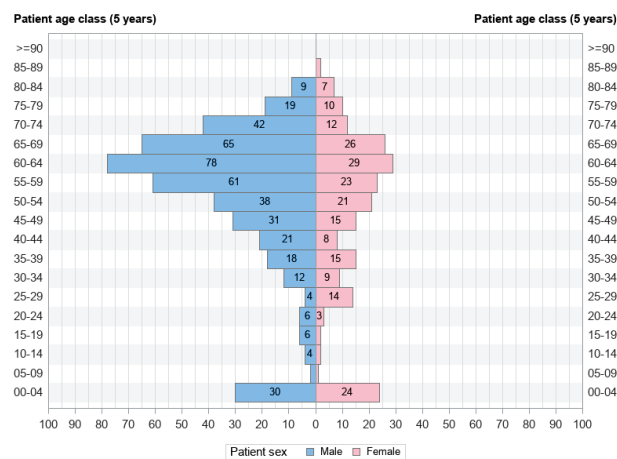
Patient Population pyramid 2016



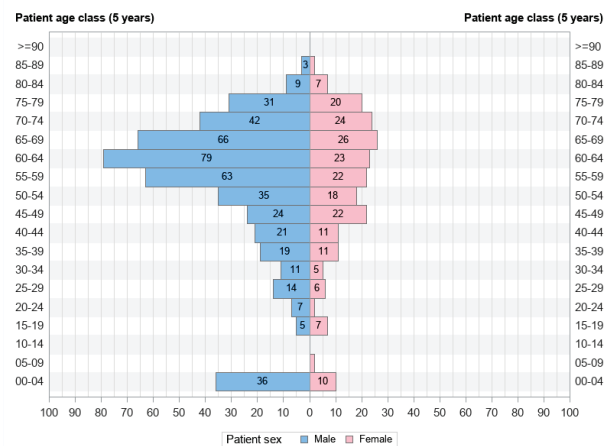
Patient Population pyramid 2017



Patient Population pyramid 2018



Patient Population pyramid 2019





## Appendix 2.3. Blood products use (2016-2019)

### Appendix 2.3.1. Billing codes for blood products delivered by stay

| Blood product                                                                                                                                                                    | VA stays (n=1422) |              | VV stays (n=379) |              | Total stays (n=1801) |              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------|------------------|--------------|----------------------|--------------|
|                                                                                                                                                                                  | N                 | %            | N                | %            | N                    | %            |
| <b>Any blood products</b>                                                                                                                                                        | <b>1216</b>       | <b>85.5%</b> | <b>336</b>       | <b>88.7%</b> | <b>1552</b>          | <b>86.2%</b> |
| 752463 Sang total et produits sanguins labiles - Concentré érythrocytaire déleucocyté : unité adulte : par unité "adulte" de concentré érythrocytaire déleucocyté, filtre inclus | 1141              | 80.2         | 318              | 83.9         | 1459                 | 81.0         |
| 752684 Concentré plaquettaire déleucocyté pathogènes-réduits : par unité de 0,5 x 10 <sup>11</sup> plaquettes                                                                    | 752               | 52.9         | 152              | 40.1         | 904                  | 50.2         |
| 752441 Sang total et produits sanguins labiles - Plasma humain frais congelé viro-inactivé : par unité de plasma humain frais congelé viro-inactivé                              | 685               | 48.2         | 128              | 33.8         | 813                  | 45.1         |
| 752581 Concentré érythrocytaire déleucocyté irradié : unité « adulte »                                                                                                           | 195               | 13.7         | 40               | 10.6         | 235                  | 13.0         |
| 752706 Concentré plaquettaire déleucocyté pathogènes-réduits : par unité de minimum 4 x 10 <sup>11</sup> plaquettes;                                                             | 21                | 1.5          | 5                | 1.3          | 26                   | 1.4          |
| 752500 Concentré plaquettaire déleucocyté (filtre inclus) : par unité de 0,5 x 10 <sup>11</sup> plaquettes                                                                       | 7                 | 0.5          | 5                | 1.3          | 12                   | 0.7          |
| 752452 Sang total et produits sanguins labiles - Concentré érythrocytaire déleucocyté : unité adulte : par unité "adulte" de concentré érythrocytaire déleucocyté, filtre inclus | 3                 | 0.2          | 0                | 0.0          | 3                    | 0.2          |
| 752673 Concentré plaquettaire déleucocyté pathogènes-réduits : par unité de 0,5 x 10 <sup>11</sup> plaquettes                                                                    | 2                 | 0.1          | 0                | 0.0          | 2                    | 0.1          |



## APPENDIX 3. USE OF ECMO IN BELGIUM: SARS-COV-2 PANDEMIC: PERIOD 2020-2022

## APPENDIX 4. REVIEW OF LITERATURE: EFFECTIVENESS AND SAFETY OF ECMO

### Appendix 4.1. Search strategy

#### Search strategy on Cochrane

|                 |                                                                                                  |     |
|-----------------|--------------------------------------------------------------------------------------------------|-----|
| Date            | 26/02/2021 16:26:18                                                                              |     |
| Database        | Cochrane                                                                                         |     |
| Search strategy |                                                                                                  |     |
| #1              | [mh "Extracorporeal Membrane Oxygenation"]                                                       | 179 |
| #2              | ((extra NEAR/1 corpor*) or extracorpor*) NEAR/3 membran*):ab,ti,kw                               | 681 |
| #3              | ecmo?:ab,ti,kw                                                                                   | 628 |
| #4              | vaECMO?:ab,ti,kw                                                                                 | 35  |
| #5              | vvECMO?:ab,ti,kw                                                                                 | 21  |
| #6              | ("extracorporeal life" NEAR/1 support?):ab,ti,kw                                                 | 53  |
| #7              | ("extra corporeal life" NEAR/1 support?):ab,ti,kw                                                | 2   |
| #8              | ecls:ab,ti,kw                                                                                    | 47  |
| #9              | ((pumpfree or "pump free" or pumpless or interventional) NEAR/3 (lung? NEAR/1 assist*)):ab,ti,kw | 6   |
| #10             | pECLA:ti,ab,kw                                                                                   | 1   |
| #11             | "extracorporeal cardiopulmonary resuscitation":ab,ti,kw                                          | 17  |
| #12             | #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11                                       | 984 |
| #13             | #1 or #12                                                                                        | 984 |
| #14             | #13 with Cochrane Library publication date Between Jan 2010 and Dec 2021                         | 804 |

**Search strategy on Embase**

|                        |                                                                                          |        |
|------------------------|------------------------------------------------------------------------------------------|--------|
| <b>Date</b>            | <b>26 Feb 2021</b>                                                                       |        |
| <b>Database</b>        | Embase                                                                                   |        |
| <b>Search strategy</b> |                                                                                          |        |
| <b>#1</b>              | 'extracorporeal oxygenation'/exp                                                         | 27629  |
| <b>#2</b>              | ((('extra corpor*' OR extracorpor*) NEAR/3 membran*):ab,ti,kw                            | 19872  |
| <b>#3</b>              | ecmo\$:ab,ti,kw                                                                          | 18513  |
| <b>#4</b>              | vaecmo\$:ab,ti,kw                                                                        | 275    |
| <b>#5</b>              | vvecmo\$:ab,ti,kw                                                                        | 178    |
| <b>#6</b>              | 'extracorporeal life support\$:ab,ti,kw                                                  | 3606   |
| <b>#7</b>              | 'extra corporeal life support\$:ab,ti,kw                                                 | 191    |
| <b>#8</b>              | ecls:ab,ti,kw                                                                            | 2488   |
| <b>#9</b>              | ((pump\$free OR pumpless OR interventional) NEAR/3 'lung\$ assist*'):ab,ti,kw            | 241    |
| <b>#10</b>             | pecla:ti,ab,kw                                                                           | 54     |
| <b>#11</b>             | 'extracorporeal cardiopulmonary resuscitation':ab,ti,kw                                  | 913    |
| <b>#12</b>             | #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11                               | 28378  |
| <b>#13</b>             | #1 OR #12                                                                                | 36709  |
| <b>#14</b>             | 'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review' | 506122 |
| <b>#15</b>             | 'biomedical technology assessment'/exp                                                   | 15082  |
| <b>#16</b>             | 'health technology assessment':ti,kw                                                     | 3090   |
| <b>#17</b>             | hta:ti,kw                                                                                | 1472   |
| <b>#18</b>             | #14 OR #15 OR #16 OR #17                                                                 | 521797 |
| <b>#19</b>             | #13 AND #18                                                                              | 923    |
| <b>#20</b>             | #19 AND [2010-2021]/py                                                                   | 830    |
| <b>#21</b>             | #20 NOT [medline]/lim                                                                    | 324    |
| <b>#22</b>             | #21 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)    | 117    |

**Search strategy on Medline**

| Date            | February 24, 2021                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |        |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| Database        | Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to February 24, 2021>                                                                                                                                                                                                                                                                                                                                                                                                                                        |        |
| Search strategy |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |        |
| 1               | Extracorporeal Membrane Oxygenation/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 11457  |
| 2               | ((extra corpor* or extracorpor*) adj3 membran*).ab,ti,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 13022  |
| 3               | ecmo?.ab,ti,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 8738   |
| 4               | vaECMO?.ab,ti,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 23     |
| 5               | vvECMO?.ab,ti,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 38     |
| 6               | extracorporeal life support?.ab,ti,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 2323   |
| 7               | extra corporeal life support?.ab,ti,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 63     |
| 8               | ecls.ab,ti,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1416   |
| 9               | ((pump?free or pumpless or interventional) adj3 lung? assist*).ab,ti,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 158    |
| 10              | pECLA.ti,ab,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 35     |
| 11              | extracorporeal cardiopulmonary resuscitation.ab,ti,kf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 575    |
| 12              | 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 16363  |
| 13              | 1 or 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 18494  |
| 14              | ((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt. | 181082 |
| 15              | meta-analys*.ti.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 123048 |
| 16              | meta-analysis.pt.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 127158 |
| 17              | exp Technology Assessment, Biomedical/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 11301  |



|    |                                                                                                                                                                 |        |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| 18 | health technology assessment.ti,kf.                                                                                                                             | 2082   |
| 19 | HtA.ti,kf.                                                                                                                                                      | 645    |
| 20 | 14 or 15 or 16 or 17 or 18 or 19                                                                                                                                | 280330 |
| 21 | 13 and 20                                                                                                                                                       | 314    |
| 22 | limit 21 to yr="2010-Current"                                                                                                                                   | 265    |
| 23 | economics/                                                                                                                                                      | 27293  |
| 24 | economics, medical/                                                                                                                                             | 9118   |
| 25 | economics, pharmaceutical/                                                                                                                                      | 2971   |
| 26 | exp economics, hospital/                                                                                                                                        | 24964  |
| 27 | economics, nursing/                                                                                                                                             | 4002   |
| 28 | economics, dental/                                                                                                                                              | 1915   |
| 29 | economics.fs.                                                                                                                                                   | 431567 |
| 30 | exp "costs and cost analysis"/                                                                                                                                  | 242793 |
| 31 | models, economic/                                                                                                                                               | 10441  |
| 32 | markov chains/                                                                                                                                                  | 14803  |
| 33 | monte carlo method/                                                                                                                                             | 29098  |
| 34 | quality-adjusted life years/                                                                                                                                    | 12945  |
| 35 | 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34                                                                                            | 575840 |
| 36 | (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf.                  | 451757 |
| 37 | (cost or costs or costing or costly).ti.                                                                                                                        | 114902 |
| 38 | cost effective*.ti,ab,kf.                                                                                                                                       | 143450 |
| 39 | (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. | 89099  |
| 40 | (decision adj1 (tree* or analy* or model*)).ti,ab,kf.                                                                                                           | 19917  |
| 41 | (markov or markow or monte carlo).ti,ab,kf.                                                                                                                     | 70170  |



|    |                                                                                |         |
|----|--------------------------------------------------------------------------------|---------|
| 42 | (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. | 28888   |
| 43 | (adjusted adj1 (quality or life)).ti,ab,kf.                                    | 18588   |
| 44 | (willing* adj2 pay).ti,ab,kf.                                                  | 7110    |
| 45 | sensitivity analys*s.ti,ab,kf.                                                 | 37932   |
| 46 | 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45                       | 775422  |
| 47 | 35 or 46                                                                       | 1106369 |
| 48 | 13 and 47                                                                      | 535     |
| 49 | limit 48 to yr="2010-Current"                                                  | 393     |

## Appendix 4.2. Appraisal of the HTA from INESSS with AMSTAR 2 criteria

|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Did the research questions and inclusion criteria for the review include the components of PICO?                                                                                                                | Yes<br><br><i>Patient</i> Adults (≥ 18 years) Adults (≥ 18 years) with cardiac or respiratory failure:<br><br><i>Intervention:</i> VV or VA ECMO<br><br><i>Comparator:</i> conventional CPR, temporary mechanical support, conventional invasive and non-invasive ventilation<br><br><i>Outcomes:</i> efficacy and safety |
| 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | Partial yes<br>The review was not registered                                                                                                                                                                                                                                                                              |
| 3. Did the review authors explain their selection of the study designs for inclusion in the review?                                                                                                                | No                                                                                                                                                                                                                                                                                                                        |
| 4. Did the review authors use a comprehensive literature search strategy?                                                                                                                                          | Yes<br>Several database were searched: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED)                                                |



|                                                                                                                                                                                                            |                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                            | Grey literature and ongoing studies were also searched.<br>Experts were consulted                                   |
| 5. Did the review authors perform study selection in duplicate?                                                                                                                                            | Yes                                                                                                                 |
| 6. Did the review authors perform data extraction in duplicate?                                                                                                                                            | Yes                                                                                                                 |
| 7. Did the review authors provide a list of excluded studies and justify the exclusions?                                                                                                                   | No                                                                                                                  |
| 8. Did the review authors describe the included studies in adequate detail?                                                                                                                                | Yes all details regarding population, intervention, comparator, study setting and timeframe follow-up are mentioned |
| 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?                                                        | Yes                                                                                                                 |
| 10. Did the review authors report on the sources of funding for the studies included in the review?                                                                                                        | No                                                                                                                  |
| 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?                                                                                  | No meta-analysis conducted                                                                                          |
| 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?                       | No meta-analysis conducted                                                                                          |
| 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?                                                                                  | Yes                                                                                                                 |
| 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?                                                             | Yes                                                                                                                 |
| 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | No meta-analysis conducted                                                                                          |
| 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?                                                            | Yes                                                                                                                 |



### Appendix 4.3. Appraisal of the meta-analysis Zhu Y et al. (Int J Clin Pract 2020) with AMSTAR 2 criteria

|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Did the research questions and inclusion criteria for the review include the components of PICO?                                                                                                                | <p>Yes</p> <p><i>Patient</i> characteristics are defined: adult subjects with severe ARDS (definition according to each author)</p> <p><i>Intervention</i> ECMO</p> <p><i>Comparator</i> conventional mechanical ventilation</p> <p><i>Outcomes</i> are coherently described with a focus on 90-days mortality as primary outcome: "Our primary outcome was 90- day mortality, and the following variables were secondary outcomes: 30-day mortality, 60-day mortality, hospital mortality, mortality at the longest duration of follow-up and device-related adverse events"</p> |
| 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | <p>Yes</p> <p>The review was registered (PROSPERO, ID = CRD42018099563)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 3. Did the review authors explain their selection of the study designs for inclusion in the review?                                                                                                                | <p>Yes (randomized controlled trials and observational studies)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 4. Did the review authors use a comprehensive literature search strategy?                                                                                                                                          | <p>Partial yes</p> <p>Six database were searched: Medline, Embase, Cochrane Library, Web of Science, Wanfang databases, CNKI. Furthermore, the reference lists from studies selected by electronic searches were screened to select other potentially eligible studies. Search terms comprised keywords, Emtree and MeSH terms. Justified publications restrictions. Full strategy is available in supplemental material.</p> <p>But authors did not search grey literature, unpublished reports or trials registries, conference abstract.</p>                                   |
| 5. Did the review authors perform study selection in duplicate?                                                                                                                                                    | <p>Yes</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 6. Did the review authors perform data extraction in duplicate?                                                                                                                                                    | <p>Yes</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |



|                                                                                                                                                                                                            |                                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7. Did the review authors provide a list of excluded studies and justify the exclusions?                                                                                                                   | Yes (with justifications)                                                                                                                                                                                                                        |
| 8. Did the review authors describe the included studies in adequate detail?                                                                                                                                | Yes all details regarding population, intervention, comparator, study setting and timeframe follow-up are mentioned                                                                                                                              |
| 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?                                                        | Yes, the Cochrane RoB tools and Newcastle-Ottawa scale (NOS) were used and the quality assessment was independently performed by two researchers.                                                                                                |
| 10. Did the review authors report on the sources of funding for the studies included in the review?                                                                                                        | No<br>"This study was supported by the Science and Technology Program of Guangzhou (201904010258). The funding bodies were not involved in the design of the study; collection, analysis and interpretation of data; and writing the manuscript" |
| 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?                                                                                  | Yes<br>Authors meta-analyzed by making the difference between randomized trials <i>versus</i> observational studies.                                                                                                                             |
| 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?                       | Yes                                                                                                                                                                                                                                              |
| 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?                                                                                  | Yes                                                                                                                                                                                                                                              |
| 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?                                                             | Yes                                                                                                                                                                                                                                              |
| 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | Yes<br>Publication bias were assessed                                                                                                                                                                                                            |
| 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?                                                            | Yes. Authors mentioned no conflict of interest                                                                                                                                                                                                   |



#### Appendix 4.4. Appraisal of the meta-analysis Wang J et al. (Heart Lung and Circulation 2021) with AMSTAR 2 criteria

|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Did the research questions and inclusion criteria for the review include the components of PICO?                                                                                                                | No<br><br><i>Patient</i> characteristics are defined: adult subjects with severe ARDS (definition according to each author)<br><br><i>Intervention</i> VV-ECMO<br><br><i>Comparator</i> conventional mechanical ventilation<br><br><i>Outcomes</i> are not clearly described and are multiple and heterogeneous: "Meaningful outcomes for patients with ARDS treated with venovenous (vv)- ECMO included mortality and the associated incidence of complications, such as 30-day mortality, 60-day mortality, 1-year mortality, ICU mortality, in-hospital mortality, and nosocomial pneumonia, haemorrhagic stroke, bleeding, and the need for continuous renal replacement therapy (CRRT)." |
| 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 3. Did the review authors explain their selection of the study designs for inclusion in the review?                                                                                                                | Yes (randomized controlled trials and observational studies)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 4. Did the review authors use a comprehensive literature search strategy?                                                                                                                                          | No<br><br>Six database were searched: Medline, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI).<br><br>Full strategy is not available<br><br>Language restriction or selection is not reported.<br><br>Authors did not search grey literature, unpublished reports or trials registries, conference abstract.                                                                                                                                                                                                                                                                                                                                        |
| 5. Did the review authors perform study selection in duplicate?                                                                                                                                                    | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 6. Did the review authors perform data extraction in duplicate?                                                                                                                                                    | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |



|                                                                                                                                                                                                            |                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 7. Did the review authors provide a list of excluded studies and justify the exclusions?                                                                                                                   | No                                                                                                                  |
| 8. Did the review authors describe the included studies in adequate detail?                                                                                                                                | Yes all details regarding population, intervention, comparator, study setting and timeframe follow-up are mentioned |
| 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?                                                        | Yes, the Cochrane RoB tools and Newcastle-Ottawa scale (NOS) were used.                                             |
| 10. Did the review authors report on the sources of funding for the studies included in the review?                                                                                                        | No                                                                                                                  |
| 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?                                                                                  | Yes                                                                                                                 |
| 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?                       | No                                                                                                                  |
| 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?                                                                                  | No                                                                                                                  |
| 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?                                                             | Yes                                                                                                                 |
| 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | No                                                                                                                  |
| 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?                                                            | Yes. Authors mentioned no conflict of interest                                                                      |



#### Appendix 4.5. Appraisal of the meta-analysis Combes A et al (Intensive Care Medicine 2020) with AMSTAR 2 criteria

|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Did the research questions and inclusion criteria for the review include the components of PICO?                                                                                                                | <p>Yes</p> <p><i>Patient</i> characteristics are defined: “patients with ARDS fulfilling the American–European Consensus Conference definition or the Berlin definition for ARDS, who were endotracheally intubated and who had signs of severe hypoxemia or hypercapnia”</p> <p><i>Intervention</i>: ECMO</p> <p><i>Comparator</i> conventional mechanical ventilation</p> <p><i>Outcomes</i> are coherently described by 90-days mortality as primary outcome:</p> <p><i>Design</i>: only RTC published after 2000</p>                                                                                                                                                                                                                                            |
| 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | <p>Yes</p> <p>The review was registered (PROSPERO, ID = CRD42019130034)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 3. Did the review authors explain their selection of the study designs for inclusion in the review?                                                                                                                | <p>Yes (randomized controlled trials): “This choice was justified by the major improvements in intensive care treatments and in ECMO technology that occurred in the last two decades.”</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 4. Did the review authors use a comprehensive literature search strategy?                                                                                                                                          | <p>Yes</p> <p>Medline, Embase and Cochrane Library were searched.</p> <p>Authors searched also other sources:</p> <p>“We also searched trial registries including ClinicalTrials.gov and the International Clinical Trial Registry Platform (ICTRP) for completed and ongoing trials. We screened conference proceedings of major critical care societies (American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), Society of Critical Care Medicine (SCCM) and International Symposium on Intensive Care and Emergency Medicine (ISICEM) for the last 5 years. We also screened reference lists of identified articles as well as systematic or narrative reviews on the topic and contact experts for further eligible trials.”</p> |
| 5. Did the review authors perform study selection in duplicate?                                                                                                                                                    | <p>Yes</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |



|                                                                                                                                                                                                            |                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 6. Did the review authors perform data extraction in duplicate?                                                                                                                                            | Yes                                                                                                                 |
| 7. Did the review authors provide a list of excluded studies and justify the exclusions?                                                                                                                   | No (but only 2 RCTs are available and were retrieved)                                                               |
| 8. Did the review authors describe the included studies in adequate detail?                                                                                                                                | Yes all details regarding population, intervention, comparator, study setting and timeframe follow-up are mentioned |
| 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?                                                        | Yes, the Cochrane RoB tool was used.                                                                                |
| 10. Did the review authors report on the sources of funding for the studies included in the review?                                                                                                        | Yes                                                                                                                 |
| 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?                                                                                  | Yes                                                                                                                 |
| 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?                       | Yes (only RCT)                                                                                                      |
| 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?                                                                                  | Yes (only RCT)                                                                                                      |
| 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?                                                             | Yes (no heterogeneity)                                                                                              |
| 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | No (not really applicable since there included two studies)                                                         |
| 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?                                                            | Yes. Authors mentioned their conflicts of interest                                                                  |



## Appendix 4.6. Forest plots from the meta-analysis Zhu F et al (Int J Clin Pract 2020) with AMSTAR 2 criteria

(A)



(B)



FIGURE 2 The 90-day mortality rates for the ECMO group and the MV group. (A) Comparison of RCT studies; (B) Comparison of observational studies



#### Appendix 4.7. Results of the use of VV-ECMO in the HTA from INESSS

| Outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Results and/or pooled risk ratio (95%CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Survival                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <ul style="list-style-type: none"><li>Combes et al. (RCT): 60-days mortality : 35% (ECMO) vs 46% (conventional ventilation); RR (95CI) : 0.76 (0.55-1.04) ; p= 0.09</li><li>Travers et al. (6 studies)<sup>a</sup>: not consistent evidence for hospital survival benefit: 1 RCT/2 with better composite outcome of 6-month (survival or severe disability); 4 observational studies/6 with improvement of hospital survival</li><li>Meta-analysis Xia et al (13 studies): OR (95CI) : 1.12 (0.69-1.81) I<sup>2</sup> : 67%</li><li>Systematic review Tillmann et al. (27 studies) : confidence in a difference in outcome between ECMO and conventional ventilation is weak given the lack of studies with appropriate control groups</li><li>Retrospective studies (3 studies): 2 studies/3 with hospital mortality decrease</li></ul> |
| <ul style="list-style-type: none"><li>The RCT from Combes <i>et al.</i> (EOLIA trial- 2018) compared VV-ECMO to conventional ventilation and did not show a significant change in 60 days mortality. However, 28% of the control-arm patients were crossed over to the intervention arm. Based on this crossover rate, authors stated that it was difficult to draw sound conclusions regarding the usefulness of ECMO.</li><li>The HTA from Travers <i>et al.</i> was based on 2 RCTs and 6 observational cohort studies. The results were not consistent and authors concluded that there was not consistent evidence for hospital survival benefit.</li><li>The meta-analysis from Xia <i>et al.</i> (that included 13 studies among which some were very old studies using devices different from current ones) did not show any benefit of ECMO in comparison to conventional ventilation. The systematic review from Tillmann <i>et al.</i> included 26 studies (seven were abstracts). Five studies had a good quality to assess the effect of VV-ECMO on outcome. Three of those studies were common with the HTA report from Travers et al (Noah 2011, Peek 2009, Pham 2013). Two studies showed a difference favouring ECMO, while three studies failed to demonstrate a significant difference between groups (results were not pooled) . Authors concluded that there was no consistent evidence (lack of good comparators, high heterogeneity). The third systematic review from Wilcox <i>et al.</i> was focused on health-related quality of life (measured with Short Form 36 tool) and not survival. It showed that the latter was reduced in patients who were treated with VV-ECMO.</li><li>Among the 3 retrospective cohort studies, 2 evidenced a lower hospital mortality among patients who were managed with VV-ECMO.</li></ul> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

<sup>a</sup> The HTA from Travers et al. mixed studies that used ECMO and pumpless extracorporeal lung assist (PECLA)



#### Appendix 4.8. Variables included in the propensity scores used in studies on cardiac arrest

| Study               | Variables included in the propensity score                                                                                                                                                                                                                                                                                                          |
|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Blumenstein (20016) | Age, gender, left ventricular ejection fraction (pre-arrest), CPR duration, and other variables not clearly mentioned ("all parameters revealed in the univariate analysis to be predictive of mortality were used in the propensity score")                                                                                                        |
| Chen (2008)         | Age, gender, initial rhythm, time-point of CPR, CPR duration, presence of comorbidities                                                                                                                                                                                                                                                             |
| Choi (2016)         | Age, year (in database), gender, comorbidities, initial rhythm, community urbanization, arrest location, witness status, bystander CPR, defibrillation, emergency department level, response time, on-scene time, transport time                                                                                                                    |
| Kim (2014)          | Age, gender, comorbidity score, bystander CPR, witnessed cardiac arrest, first documented arrest rhythm, presumed etiology of arrest, interval from arrest to CPR started by emergency medical services provider, CPR duration, and therapeutic hypothermia                                                                                         |
| Maekawa (2013)      | All included variables are not clearly mentioned ("All baseline prehospital characteristics that varied between the ECPR and CCPR groups at a p value less than 0.10, and which were potentially related to outcome": age, gender, initial rhythm, CPR by witness,) with addition of percutaneous coronary intervention and therapeutic hypothermia |
| Shin (2013)         | Age, gender, study period, ICU severity scores and CPR characteristics (cause, initial rhythm, duration, time zone)                                                                                                                                                                                                                                 |

Legend: CPR: cardiopulmonary resuscitation

#### Appendix 4.9. Appraisal of the systematic review and meta-analysis from HTA Ontario with AMSTAR 2 criteria

|                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Did the research questions and inclusion criteria for the review include the components of PICO? | Yes<br><br><i>Patient</i> Adults ( $\geq 18$ years) with cardiac arrest that is refractory to conventional cardiopulmonary resuscitation, or Adults ( $\geq 18$ years) with cardiogenic shock that is refractory to conventional medical management: drugs, mechanical support<br><br><i>Intervention</i> ECMO<br><br><i>Comparator</i> CPR or conventional treatment of cardiogenic shock |
|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|



|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                    | <i>Outcomes</i> are coherently described: survival 30 days and beyond, neurological outcome, others outcome (length of stay, weaning of ECMO, complications,...)                                                                                                                                                                                                                                                                                                                                                                                                   |
| 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | Yes<br>The review was registered (PROSPERO, ID = CRD 42018117477)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 3. Did the review authors explain their selection of the study designs for inclusion in the review?                                                                                                                | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 4. Did the review authors use a comprehensive literature search strategy?                                                                                                                                          | Yes<br>Several database were searched: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED)<br>Grey literature and ongoing studies were also searched.<br>Experts were consulted (list in acknowledgement section)                                                                                                                                                                  |
| 5. Did the review authors perform study selection in duplicate?                                                                                                                                                    | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 6. Did the review authors perform data extraction in duplicate?                                                                                                                                                    | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 7. Did the review authors provide a list of excluded studies and justify the exclusions?                                                                                                                           | Yes (with justifications)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 8. Did the review authors describe the included studies in adequate detail?                                                                                                                                        | Yes all details regarding population, intervention, comparator, study setting and timeframe follow-up are mentioned                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?                                                                | Yes<br>"We assessed risk of bias using the Risk of Bias in Systematic Reviews (ROBIS) tool for systematic reviews and the Risk of Bias Among Nonrandomized Trials (ROBINS-I) tool for observational studies. (Appendix 2).19,20<br>We evaluated the quality of the body of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook. The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias." |
| 10. Did the review authors report on the sources of funding for the studies included in the review?                                                                                                                | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |



|                                                                                                                                                                                                            |                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?                                                                                  | Yes                                                                                          |
| 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?                       | Yes                                                                                          |
| 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?                                                                                  | Yes                                                                                          |
| 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?                                                             | Yes                                                                                          |
| 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | No but authors checked the ongoing clinical trials potentially relevant in ClinicalTrial.gov |
| 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?                                                            | Yes (government agency)                                                                      |

#### Appendix 4.10. Appraisal of the systematic review and meta-analysis from Miraglia et al J(ournal of American College of Emergency Physicians Open 2020) with AMSTAR 2 criteria

|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Did the research questions and inclusion criteria for the review include the components of PICO?                                                                                                                | Yes<br><br><i>Patient</i> characteristics are defined: adults resuscitated from in- and out-of-hospital cardiac arrest<br><br><i>Intervention</i> ECMO -ECPR<br><br><i>Comparator</i> conventional CPR<br><br><i>Outcomes</i> are coherently described: rates of 30-day and long-term favorable neurological outcome and survival |
| 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | Yes<br>The review was registered (PROSPERO, ID = CRD42020158758)                                                                                                                                                                                                                                                                  |



|                                                                                                                                                                                                            |                                                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| 3. Did the review authors explain their selection of the study designs for inclusion in the review?                                                                                                        | Yes (propensity score matched and justification is provided in the discussion section)                                  |
| 4. Did the review authors use a comprehensive literature search strategy?                                                                                                                                  | Yes partially (lack consultation of experts and grey literature) Databases were Medline, Embase, Scopus, Google Scholar |
| 5. Did the review authors perform study selection in duplicate?                                                                                                                                            | Yes                                                                                                                     |
| 6. Did the review authors perform data extraction in duplicate?                                                                                                                                            | Yes                                                                                                                     |
| 7. Did the review authors provide a list of excluded studies and justify the exclusions?                                                                                                                   | No                                                                                                                      |
| 8. Did the review authors describe the included studies in adequate detail?                                                                                                                                | Yes all details regarding population, intervention, comparator, study setting and timeframe follow-up are mentioned     |
| 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?                                                        | Yes, the Newcastle-Ottawa scale (NOS) was used.                                                                         |
| 10. Did the review authors report on the sources of funding for the studies included in the review?                                                                                                        | No                                                                                                                      |
| 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?                                                                                  | Yes                                                                                                                     |
| 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?                       | No                                                                                                                      |
| 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?                                                                                  | Yes                                                                                                                     |
| 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?                                                             | Yes                                                                                                                     |
| 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | Yes<br>Publication bias was assessed                                                                                    |
| 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?                                                            | Yes Authors mentioned no conflict of interest                                                                           |



### Appendix 4.11. Studies on cardiac arrest included in the systematic reviews and meta-analysis

| Authors               | Miraglia et al.<br>2020 | Chen et al.<br>2019 | Twohig et al.<br>2019 | Ontario Health<br>2020 |
|-----------------------|-------------------------|---------------------|-----------------------|------------------------|
| Blumenstein<br>(2016) | +                       | +                   | +                     | +                      |
| Chen<br>(2008)        | /                       | +                   | /                     | +                      |
| Choi<br>(2016)        | +                       | +                   | +                     | +                      |
| Chou<br>(2014)        | /                       | +                   | +                     | +                      |
| Kim<br>(2014)         | +                       | +                   | +                     | +                      |
| Lee<br>(2015)         | /                       | +                   | +                     | +                      |
| Lin<br>(2010)         | /                       | +                   | /                     | /                      |
| Maekawa<br>(2013)     | +                       | +                   | +                     | +                      |
| Sakamoto<br>(2014)    | /                       | +                   | +                     | +                      |
| Schober<br>(2017)     | /                       | +                   | /                     | /                      |
| Shin*<br>(2011)       | /                       | +                   | /                     | /                      |
| Shin*<br>(2013)       | +                       | +                   | +                     | +                      |
| Siao<br>(2015)        | /                       | +                   | +                     | +                      |

Legend: \* report on the same cohort



#### Appendix 4.12. Appraisal of the systematic review and meta-analysis from Twohig et al. Journal of Intensive Care Society 2019 with AMSTAR-2 criteria

|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Did the research questions and inclusion criteria for the review include the components of PICO?                                                                                                                | Yes<br><br>'In adult patients of cardiac-origin cardiac arrest (P), does extracorporeal-CPR (I), compared to conventional-CPR (C), improve survival and neurological outcome (O) as illustrated by cohort studies (S) published in the years 2011–2017 (T)'                                         |
| 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | No                                                                                                                                                                                                                                                                                                  |
| 3. Did the review authors explain their selection of the study designs for inclusion in the review?                                                                                                                | No                                                                                                                                                                                                                                                                                                  |
| 4. Did the review authors use a comprehensive literature search strategy?                                                                                                                                          | Partially yes<br>Searched databases were: Medline (Pubmed), Embase, Web of Science<br>Search terms comprised keywords, available in the supplements section.<br>Grey literature, reports of societies, were consulted.<br>Consultation of experts in the field and ongoing trials are not mentioned |
| 5. Did the review authors perform study selection in duplicate?                                                                                                                                                    | Yes                                                                                                                                                                                                                                                                                                 |
| 6. Did the review authors perform data extraction in duplicate?                                                                                                                                                    | No                                                                                                                                                                                                                                                                                                  |
| 7. Did the review authors provide a list of excluded studies and justify the exclusions?                                                                                                                           | No                                                                                                                                                                                                                                                                                                  |
| 8. Did the review authors describe the included studies in adequate detail?                                                                                                                                        | Yes                                                                                                                                                                                                                                                                                                 |



|                                                                                                                                                                                                            |                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?                                                        | Yes                                       |
| 10. Did the review authors report on the sources of funding for the studies included in the review?                                                                                                        | No                                        |
| 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?                                                                                  | No                                        |
| 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?                       | No                                        |
| 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?                                                                                  | Yes                                       |
| 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?                                                             | Yes                                       |
| 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | No                                        |
| 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?                                                            | Authors mentioned no conflict of interest |



#### Appendix 4.13. Appraisal of the systematic review and meta-analysis from Chen Z et al. (Biomed research Intern 2019) with AMSTAR-2 criteria

|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Did the research questions and inclusion criteria for the review include the components of PICO?                                                                                                                | Yes                                                                                                                                                                                                                                                        |
| 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | Yes<br>Registered in PROSPERO ID CRD42018100513                                                                                                                                                                                                            |
| 3. Did the review authors explain their selection of the study designs for inclusion in the review?                                                                                                                | No                                                                                                                                                                                                                                                         |
| 4. Did the review authors use a comprehensive literature search strategy?                                                                                                                                          | Partially yes<br>Searched databases were: PubMed, Cochrane Library, ISI Web of Knowledge, and Embase<br>Search terms comprised keywords clearly indicated<br>Grey literature and consultation of experts in the field and ongoing trials are not mentioned |
| 5. Did the review authors perform study selection in duplicate?                                                                                                                                                    | Yes                                                                                                                                                                                                                                                        |
| 6. Did the review authors perform data extraction in duplicate?                                                                                                                                                    | Yes                                                                                                                                                                                                                                                        |
| 7. Did the review authors provide a list of excluded studies and justify the exclusions?                                                                                                                           | No                                                                                                                                                                                                                                                         |
| 8. Did the review authors describe the included studies in adequate detail?                                                                                                                                        | Yes (table of evidence in Supplementary section)                                                                                                                                                                                                           |
| 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?                                                                | Yes                                                                                                                                                                                                                                                        |
| 10. Did the review authors report on the sources of funding for the studies included in the review?                                                                                                                | No                                                                                                                                                                                                                                                         |
| 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?                                                                                          | Yes                                                                                                                                                                                                                                                        |



|                                                                                                                                                                                                            |                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?                       | Yes                                       |
| 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?                                                                                  | Yes                                       |
| 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?                                                             | Yes                                       |
| 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | Yes                                       |
| 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?                                                            | Authors mentioned no conflict of interest |

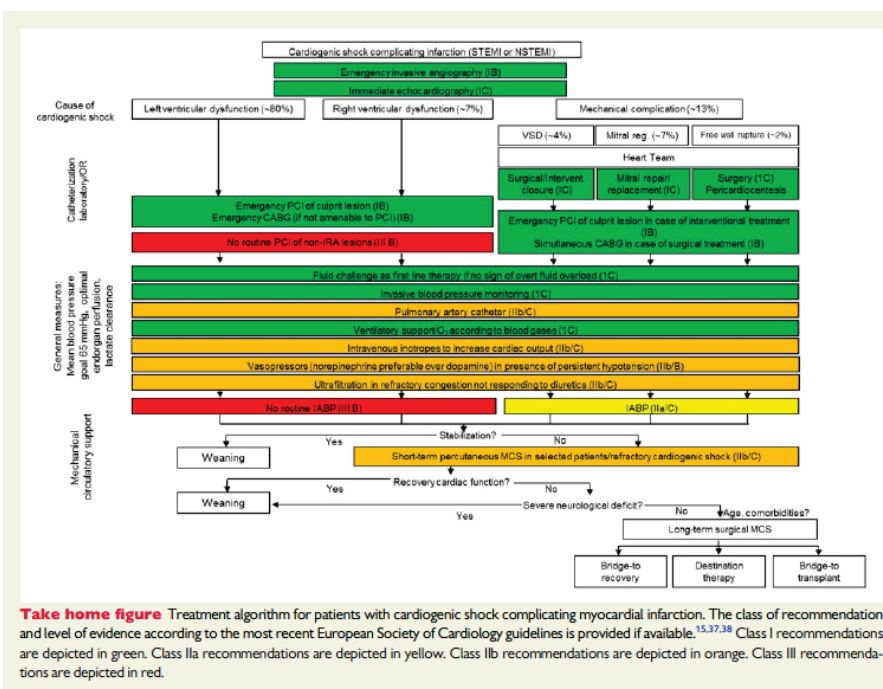
#### Appendix 4.14. Neurological scores to determine favourable neurological outcome after cardiac arrest

| Modified Glasgow outcome scale | Neurological outcome                                                          |
|--------------------------------|-------------------------------------------------------------------------------|
| 0                              | Patient died with unknown cerebral status                                     |
| 1                              | Patient died with documented hypoxic brain damage                             |
| 2                              | Persistent vegetative state (unable to interact with environment)             |
| 3                              | Severe disability (unable to live independently but able to follow commands)  |
| 4                              | Moderate disability (able to live independently but unable to return to work) |
| 5                              | Mild or no disability (able to return to work)                                |



| Cerebral Performance Category | Neurological outcome         |
|-------------------------------|------------------------------|
| 1                             | Good cerebral performance    |
| 2                             | Moderate cerebral disability |
| 3                             | Sever cerebral disability    |
| 4                             | Coma or vegetative state     |
| 5                             | Brain death                  |

#### Appendix 4.15. Management of cardiogenic shock Guidelines from European Society of Cardiology (2019)





## **APPENDIX 5. REVIEW OF LITERATURE: ORGANIZATION OF ECMO SERVICES**

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## APPENDIX 6. INTERNATIONAL COMPARISON ON THE USE AND FUNDING OF ECMO

### Appendix 6.1.

#### Clinical organization

1. Is the use of ECMO centralized at a nationwide level?
1. If YES, is there a Board of people leading this project?
2. If YES, could you please describe the characteristics of this Board (number; selection; expertise – ICU physicians, surgeons, perfusionists, economists etc.)
3. What are the requirements of hospitals to organize an ECMO program?
  - Specific training for doctors and nurses
  - Ratio of doctor and/or nurses per patient (if YES, which is this ratio)
  - Interdependence with other hospital departments (24/7 cardiothoracic surgery and/or vascular required)
  - 24/7 available perfusionist
  - 24/7 available doctor expert in ECMO
  - Minimum monitoring (hemodynamic, respiratory, neurological ...)
  - Continuous education (certificate renewal)
  - Threshold number of ECMO per year
  - Morbidity-mortality discussion
  - Quality process
  - ECMO Mobile Unit
  - Report of data to a National institution (Health Minister, Reimbursement Department ...)
  - Report of data to an International database (ELSO)
4. Can an ECMO center be authorized only for VV but not for VA support ?
5. Does a national ECMO registry/statistics exist?
  - If YES, are any of these data on use publicly available and if so, could you indicate where we could access them?
  - If YES, is there an information transfer between centers to provide information on availability of ECMO at any moment?
6. Do the country have mobile ECMO?



- If yes, how many exists overall and how was this number determined (eg min per X km<sup>2</sup>)
- How are transfers organized? (which hospital: applicant or recipient hospital, how many kilometers, evaluation of indication, surface area, ambulance network, team for transport: ECMO consultant, nurse, perfusionist)

### **Economical organization**

1. How is the reimbursement/funding of ECMO organized in your country?:

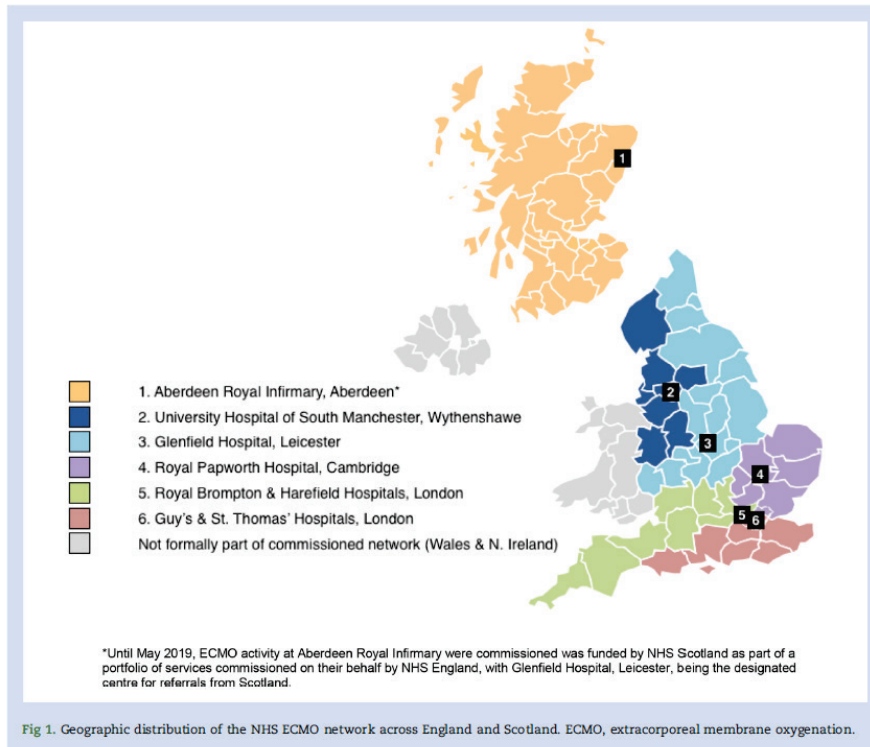
- Lump sum reimbursement for the use of ECMO overall (including all aspects?). If so, is this a one-off lump sum? And how much is this? Does it vary depending on the type of ECMO (VV, VA? And or the type of patient/diagnosis?). If so how?
- Is there a separate payment/reimbursement for the disposables? If so, how much is it and what does it cover specifically?
- Frequency of reimbursement: daily, single?
- Are any other aspects reimbursed/funded separately? Eg monitoring once ECMO is in place, ECMO related lab tests? Any other costs?

2. How much does ECMO cost on average to the hospital? Please specify what the cost mentioned represents (eg. Annual cost of ECMO. Per patient cost. Etc.)

3. Which medical specialties are authorized to use/implant ECMO? Are there any limitations, or conditional reimbursement on this regard?



## Appendix 6.2. Providers of ECMO services in The United Kingdom

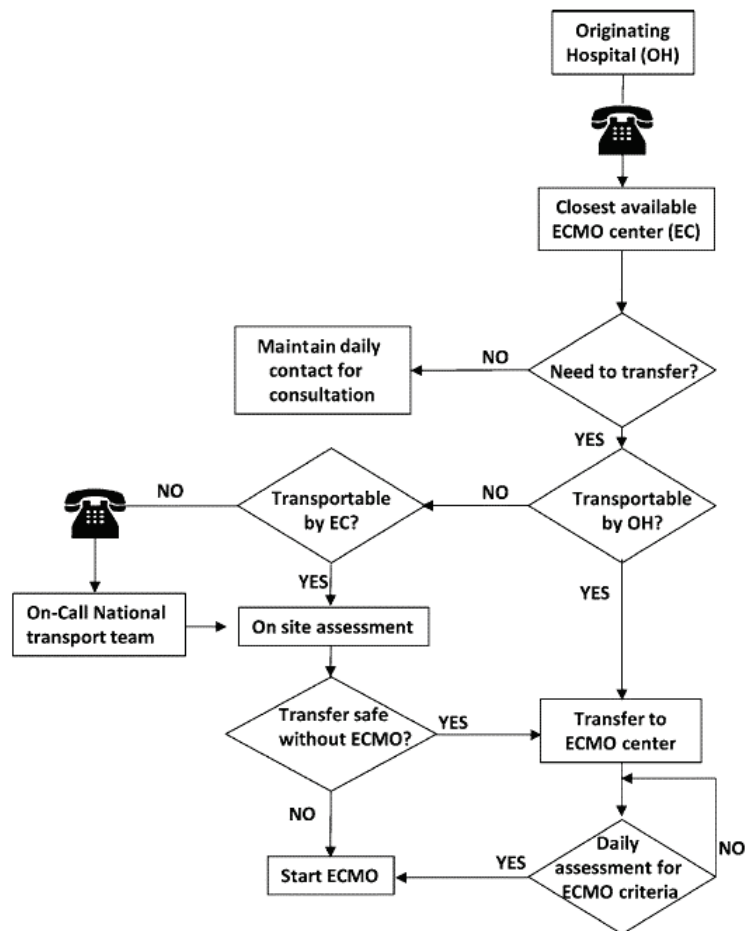




### Appendix 6.3. Characteristics of ECMO centres included in the Italian network ECMOnet at its onset

| City     | Institution                                                                       | Geographical Location | ICU capacity | ECMO capacity |  | Transport Coverage |
|----------|-----------------------------------------------------------------------------------|-----------------------|--------------|---------------|--|--------------------|
| Bari     | Ospedale Policlinico, Università di Bari                                          | South                 | 16           | 2             |  | Regional           |
| Bergamo  | Ospedali Riuniti di Bergamo                                                       | North                 | 16           | 2             |  | Regional           |
| Bologna  | Ospedale S. Orsola-Malpighi, Università di Bologna                                | North                 | 12           | 2             |  | Regional           |
| Florence | Ospedale Careggi, Università di Firenze                                           | Center                | 10           | 4             |  | Regional           |
| Milan    | Ospedale Maggiore Policlinico, Mangiagalli and Regina Elena, Università di Milano | North                 | 6            | 2             |  | National           |
| Milan    | Ospedale San Raffaele, Università Vita-Salute San Raffaele                        | North                 | 14           | 7             |  | National           |
| Monza    | Ospedale San Gerardo, Università Milano-Bicocca                                   | North                 | 10           | 4             |  | National           |
| Naples   | Ospedale Federico II, Università di Napoli                                        | South                 | 14           | 3             |  | Regional           |
| Padua    | Azienda Ospedaliera Universitaria di Padova                                       | North                 | 11           | 4             |  | Regional           |
| Palermo  | Istituto Mediterraneo per i Trapianti e Terapie ad alta Specializzazione          | South                 | 14           | 6             |  | Regional           |
| Pavia    | Fondazione IRCCS Policlinico San Matteo, Università degli Studi di Pavia          | North                 | 20           | 6             |  | National           |
| Rome     | Ospedale A. Gemelli, Università La Sapienza                                       | Center                | 18           | 1             |  | Regional           |
| Rome     | Policlinico Umberto I, Università Cattolica del Sacro Cuore                       | Center                | 18           | 2             |  | Regional           |
| Turin    | Ospedale San Giovanni Battista-Molinette, Università di Torino                    | North                 | 14           | 7             |  | National           |

## APPENDIX 6.4. Algorithm for the referrals in the Italian network



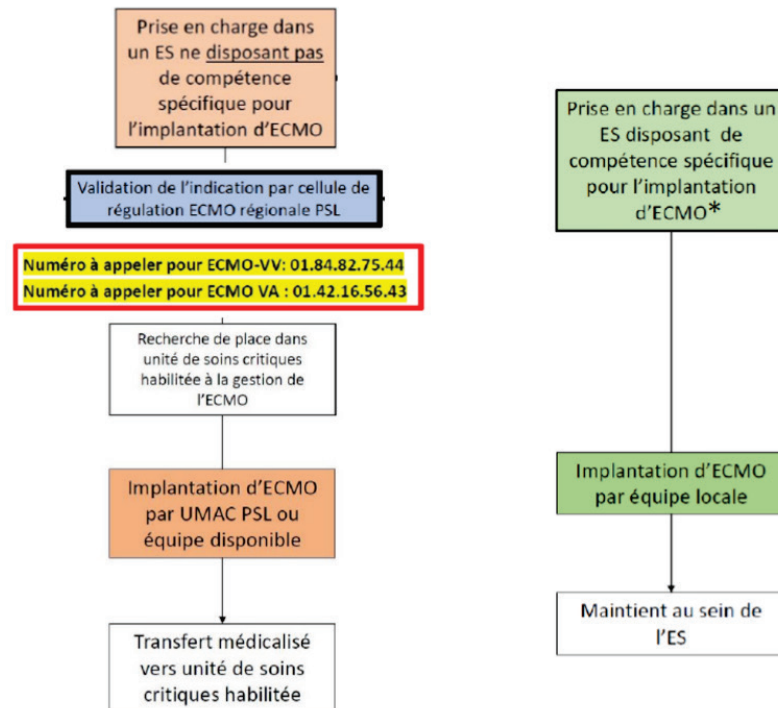


### Appendix 6.5. List of retrieved formation session

| Name                                                                                                | Place    | URL                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------------------------------------------------|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ECMO diploma                                                                                        | Paris    | <a href="https://www.paris-tcsecmo.org/">https://www.paris-tcsecmo.org/</a>                                                                                                                                                                                                                                                   |
| Diplôme d'Université Circulation extra-corporelle en chirurgie cardiaque et en suppléance d'organes | Bordeaux | <a href="https://www.u-bordeaux.fr/formation/2020/PRSUF04_71/diplome-d-universite-circulation-extra-corporelle-en-chirurgie-cardiaque-et-en-suppleance-d-organes">https://www.u-bordeaux.fr/formation/2020/PRSUF04_71/diplome-d-universite-circulation-extra-corporelle-en-chirurgie-cardiaque-et-en-suppleance-d-organes</a> |
| Suppléance hémodynamique et organes artificiels en réanimation                                      | Lyon     | <a href="http://offre-de-formations.univ-lyon1.fr/parcours-850/suppleance-hemodynamique-et-organes-artificiels-en-reanimation.html#">http://offre-de-formations.univ-lyon1.fr/parcours-850/suppleance-hemodynamique-et-organes-artificiels-en-reanimation.html#</a>                                                           |
| Formation à l'ECMO par la simulation                                                                | Angers   | <a href="https://www.all-sims.fr/formation-a-lecmo-par-la-simulation/">https://www.all-sims.fr/formation-a-lecmo-par-la-simulation/</a>                                                                                                                                                                                       |
| European Society of Intensive Care Medicine (ESICM): ECMO Master class                              | Online   | <a href="https://www.esicm.org/wp-content/uploads/2021/12/ECMO-Programme_2022-webpage-V2.pdf">https://www.esicm.org/wp-content/uploads/2021/12/ECMO-Programme_2022-webpage-V2.pdf</a>                                                                                                                                         |
| ECMO edays International Symposium on intensive care and emergency medicine (ISICEM)                | Online   | <a href="https://www.isicem.org/17/main.asp?ety=17&amp;eventid=1079190630">https://www.isicem.org/17/main.asp?ety=17&amp;eventid=1079190630</a>                                                                                                                                                                               |



## Appendix 6.6. Algorithm for the referral in ECMO centres from the region of Paris during the SARS-CoV-2 pandemic



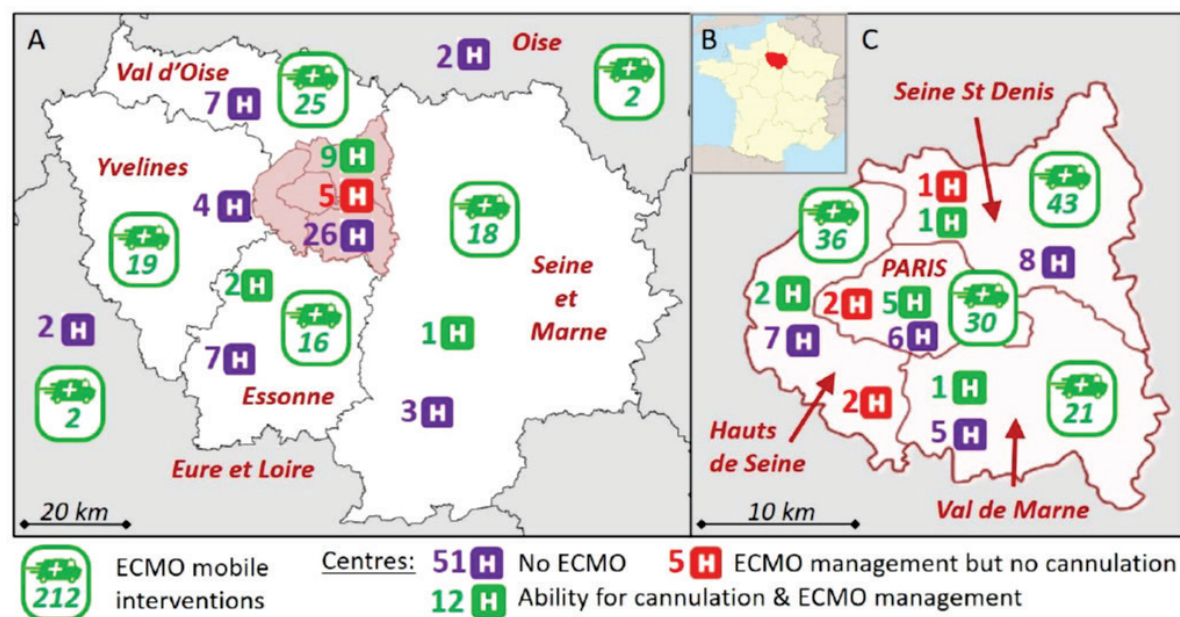
\* Centres ayant la capacité de mise en place et de gestion en réanimation d'une ECMO pour COVID :  
Bichat (01 40 25 60 09), Henri Mondor (01 49 81 49 00), HEGP (01 56 09 25 00), NECKER SAMU 75 (01 44 49 40 00), Foch (01.46 25 22 24 / 01 46 25 59 31), CCN (01 49 33 48 49), CMCL Marie Lannelongue (01 40 94 25 85), Montsouris IMM (01.56.61.68.34), Jacques Cartier Massy (06 07 50 03 19).

Responsable ECMO gestion de crise : Dr Guillaume Lebreton ([g.lebreton@sftctv.fr](mailto:g.lebreton@sftctv.fr) / [guillaume.lebreton@aphp.fr](mailto:guillaume.lebreton@aphp.fr))



### Appendix 6.7. Map of ECMO centralisation in the region of 'Great Paris'

**Figure S4: Map of the Greater Paris reporting the mobile extracorporeal membrane oxygenation team activity, and the number of hospitals where patients were cannulated**





## Appendix 6.8. Estimation of total hospital costs of patients on ECMO support in the University Medical Centre Groeningen

**TABLE 2. Total Hospital Costs of All Patients (*n* = 67)**

| Resource Quantity                           | Mean (sd)        | % of Total | Median | Minimum | Maximum |
|---------------------------------------------|------------------|------------|--------|---------|---------|
| Nursing days                                | 55,464 (64,357)  | 52         | 31,155 | 2,377   | 334,068 |
| Extracorporeal life support procedural cost | 11,874 (2,129)   | 11         | 11,369 | 10,117  | 20,764  |
| Other resource quantities                   | 38,924 (34,520)  | 37         | 34,000 | 1,792   | 200,195 |
| Functional examinations                     | 2,009 (2,644)    | 2          | 1,033  | 0       | 11,525  |
| Imaging                                     | 2,146 (2,317)    | 2          | 1,390  | 0       | 10,412  |
| Transplantation                             | 1,774            | 2          | 0      | 0       | 22,890  |
| Renal replacement therapy                   | 3,755 (9,323)    | 4          | 598    | 0       | 57,723  |
| Screening                                   | 23 (83)          | 0          | 0      | 0       | 531     |
| Other                                       | 706 (1,255)      | 1          | 0      | 0       | 7,127   |
| Surgeries                                   | 13,105 (12,000)  | 12         | 13,573 | 0       | 48,420  |
| Anesthesiology                              | 163 (3,514)      | 0          | 0      | 0       | 1,229   |
| Laboratory                                  | 3,655 (3,514)    | 3          | 0      | 243     | 17,253  |
| Microbiology                                | 4,071 (5,600)    | 4          | 2,267  | 0       | 34,454  |
| Blood products                              | 7,511 (8,565)    | 7          | 4,467  | 0       | 51,892  |
| Total                                       | 106,263 (95,933) |            | 83,751 | 14,580  | 546,572 |

All costs are in Euros.



## APPENDIX 7. SYSTEMATIC LITERATURE REVIEW OF COSTING STUDIES ON ECMO

### Appendix 7.1. Search Strategies on ECMO costing studies

#### *Appendix 7.1.1. Search strategy on MEDLINE*

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to February 24, 2021>

- 
- 1 Extracorporeal Membrane Oxygenation/ (11457)
  - 2 ((extra corpor\* or extracorpor\*) adj3 membran\*).ab,ti,kf. (13022)
  - 3 ecmo?.ab,ti,kf. (8738)
  - 4 vaECMO?.ab,ti,kf. (23)
  - 5 vvECMO?.ab,ti,kf. (38)
  - 6 extracorporeal life support?.ab,ti,kf. (2323)
  - 7 extra corporeal life support?.ab,ti,kf. (63)
  - 8 ecls.ab,ti,kf. (1416)
  - 9 ((pump?free or pumpless or interventional) adj3 lung? assist\*).ab,ti,kf. (158)
  - 10 pECLA.ti,ab,kf. (35)
  - 11 extracorporeal cardiopulmonary resuscitation.ab,ti,kf. (575)
  - 12 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (16363)
  - 13 1 or 12 (18494)
  - 14 ((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt. (181082)
  - 15 meta-analys\*.ti. (123048)



- 16 meta-analysis.pt. (127158)
- 17 exp Technology Assessment, Biomedical/ (11301)
- 18 health technology assessment.ti,kf. (2082)
- 19 HtA.ti,kf. (645)
- 20 14 or 15 or 16 or 17 or 18 or 19 (280330)
- 21 13 and 20 (314)
- 22 limit 21 to yr="2010-Current" (265)
- 23 economics/ (27293)
- 24 economics, medical/ (9118)
- 25 economics, pharmaceutical/ (2971)
- 26 exp economics, hospital/ (24964)
- 27 economics, nursing/ (4002)
- 28 economics, dental/ (1915)
- 29 economics.fs. (431567)
- 30 exp "costs and cost analysis"/ (242793)
- 31 models, economic/ (10441)
- 32 markov chains/ (14803)
- 33 monte carlo method/ (29098)
- 34 quality-adjusted life years/ (12945)
- 35 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (575840)
- 36 (econom\* or price or prices or pricing or priced or discount\* or expenditure\* or budget\* or pharmacoeconomic\* or pharmaco-economic\*).ti,ab,kf. (451757)
- 37 (cost or costs or costing or costly).ti. (114902)
- 38 cost effective\*.ti,ab,kf. (143450)



- 39 (cost\* adj2 (util\* or efficacy\* or benefit\* or minimi\* or analy\* or saving\* or estimate\* or allocation or control or sharing or instrument\* or technolog\*)),ab.  
(89099)
- 40 (decision adj1 (tree\* or analy\* or model\*)),ti,ab,kf. (19917)
- 41 (markov or markow or monte carlo).ti,ab,kf. (70170)
- 42 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (28888)
- 43 (adjusted adj1 (quality or life)).ti,ab,kf. (18588)
- 44 (willing\* adj2 pay).ti,ab,kf. (7110)
- 45 sensitivity analys\*s.ti,ab,kf. (37932)
- 46 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (775422)
- 47 35 or 46 (1106369)
- 48 13 and 47 (535)
- 49 limit 48 to yr="2010-Current" (393)

### *Appendix 7.1.2. Search strategy on Embase*

#### **26 February 2021**

| No. | Query                                                                                                                                          | Results |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| #38 | #37 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)                                                          | 127     |
| #37 | #36 NOT [medline]/lim                                                                                                                          | 578     |
| #36 | #35 AND [2010-2021]/py                                                                                                                         | 1272    |
| #35 | #13 AND #34                                                                                                                                    | 1512    |
| #34 | #24 OR #33                                                                                                                                     | 1780695 |
| #33 | #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32                                                                                           | 1255697 |
| #32 | (((adjusted NEAR/2 (quality OR life)):ab,ti,tn,kw) OR ((willing* NEAR/2 pay):ab,ti,tn,kw) OR sensitivity:ab,ti,tn,kw) AND analys*s:ab,ti,tn,kw | 369330  |



- #31 qoly:ab,ti,tn,kw OR qolys:ab,ti,tn,kw OR hrqol:ab,ti,tn,kw OR hrqols:ab,ti,tn,kw OR qaly:ab,ti,tn,kw OR qalys:ab,ti,tn,kw OR qale:ab,ti,tn,kw OR qales:ab,ti,tn,kw 49994
- #30 (markov:ab,ti,tn,kw OR markow:ab,ti,tn,kw OR monte:ab,ti,tn,kw) AND carlo:ab,ti,tn,kw 52640
- #29 (decision NEAR/1 (tree\* OR analy\* OR model\*)):ab,ti,tn,kw 29180
- #28 (cost\* NEAR/2 (util\* OR efficac\* OR benefit\* OR minimi\* OR analy\* OR saving\* OR estimate\* OR allocation OR control OR sharing OR instrument\* OR technolog\*)):ab 136211
- #27 'cost effective\*':ab,ti,tn,kw 198054
- #26 cost:ti OR costs:ti OR costing:ti OR costly:ti 157474
- #25 econom\*:ab,ti,tn,kw OR price:ab,ti,tn,kw OR prices:ab,ti,tn,kw OR pricing:ab,ti,tn,kw OR priced:ab,ti,tn,kw OR discount\*:ab,ti,tn,kw OR expenditure\*:ab,ti,tn,kw OR budget\*:ab,ti,tn,kw OR pharmacoeconomic\*:ab,ti,tn,kw OR 'pharmaco economic\*':ab,ti,tn,kw 567635
- #24 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 913217
- #23 'monte carlo method'/de 42345
- #22 'quality-adjusted life years'/de 28234
- #21 'cost'/exp 363111
- #20 'economic evaluation'/exp 315162
- #19 'economic aspect'/de 134260
- #18 'drug formulary'/de 3413
- #17 'drug cost'/de 78996
- #16 'pharmacoeconomics'/de 7513
- #15 'health economics'/de 40229
- #14 'economics'/de 243150
- #13 #1 OR #12 36713
- #12 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 28383
- #11 'extracorporeal cardiopulmonary resuscitation':ab,ti,kw 913
- #10 pecla:ti,ab,kw 54



#9 ((pump\$free OR pumpless OR interventional) NEAR/3 'lung\$ assist\*'):ab,ti,kw 241  
 #8 ecls:ab,ti,kw 2488  
 #7 'extra corporeal life support\$:ab,ti,kw 191  
 #6 'extracorporeal life support\$:ab,ti,kw 3606  
 #5 vvecmo\$:ab,ti,kw 178  
 #4 vaecmo\$:ab,ti,kw 275  
 #3 ecmo\$:ab,ti,kw 18513  
 #2 (('extra corpor\*' OR extracorpor\*) NEAR/3 membran\*):ab,ti,kw 19872  
 #1 'extracorporeal oxygenation'/exp 27629

## Appendix 7.2. Assumptions for estimations on mean daily costs for ECMO per patient from literature

### Costing extraction and assumptions made (if needed) to estimate the mean daily costs of ECMO from identified costing studies

| Author              | Costing yr | Updated daily costs<br>Feb 2022 (in €) | Costs and assumptions (when needed) to estimate daily costs of ECMO from the literature                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------|------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Peek</b>         | 2005       | <b>€7657</b>                           | ECMO daily costs estimated as the difference in costs between the ECMO and the non-ECMO arms (incremental costs). Costs cover 6 months and include transport and outpatient costs as well as inpatient costs for that period. These were GBP 40 544 over the whole studies period. The median duration of ECMO was 9 days.                                                                                                                                                                                                                                                                    |
| <b>Mishra</b>       | 2007       | <b>€8472</b>                           | Estimations based on mean incremental costs in the ICU for ECMO, over non-ECMO ICU patients (US\$ 67 000). The mean ECMO duration was 9,5 days.                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Oude-Lansink</b> | 2013       | <b>€2460</b>                           | Estimation based on the mean cost of ECMO procedure and daily surcharge over hospital admission (nursing days excluded from the estimation, since no split between ECMO/non-ECMO ICU patients). These costs were €11 948. The mean duration of ECMO was 135 hrs/24 (~5,625 days).                                                                                                                                                                                                                                                                                                             |
| <b>Minshra</b>      | 2012       | <b>€16 575</b>                         | ECMO costs: US\$15 000/day. Personnel costs US\$5910; surgical supplies US\$9000. Duration of ECMO 8+/-7 days. These costs represent the overall costs for the episode.                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Barret</b>       | 2016       | <b>€10 091</b>                         | Estimated as the difference between the cost for conventional ventilation and the costs of ECMO (over 6 months). The original costs were taken from Peek et al 2006, but it was assumed that the 24% of patients who should have got ECMO in the trial but didn't, did get it. The overall incremental costs over 6 months were €117 369. The authors did not give information on the assumptions regarding ECMO duration or LoS. Since they took the original costs from Peek et al., an assumption was made that the duration of ECMO was also taken from the same source (median: 9 days). |
| <b>Fernando</b>     | 2016       | <b>€9409</b>                           | Estimate for the median inpatient care costs with ECMO over 1 year (non-comparative, therefore no incremental costs). These costs were CAN\$91 192. No ECMO duration was available. Daily costs resulting from dividing the median costs by an assumed duration of 7,5                                                                                                                                                                                                                                                                                                                        |



days. Since the duration of ECMO was not mentioned in the article, the assumption was based on the average between the mean duration of VV-ECMO (9 days) and VA-ECMO (6 days) from the other articles included in our review. An assumption was made in this case, that most costs were specifically linked to the ECMO.

|                        |      |              |                                                                                                                                                                                                                                                                                                                             |
|------------------------|------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Dennis</b>          | 2016 | <b>€4294</b> | Estimate for the mean incremental overall costs AU\$21 758 (for the entire analysed period). The mean ECMO duration was 3,8 days.                                                                                                                                                                                           |
| <b>Jaamaa-Holmberg</b> | 2017 | <b>€3561</b> | Since overall costs mentioned in this study included ward day-costs of the patient's care in different units, surgical procedures, and laboratory and imaging costs, only the quoted mean ICU day-price of VA ECMO treated patients in 2017 was considered. This was €3363 per day. The median VA ECMO duration was 6 days. |



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2. Poptsov V, Spirina E, Dogonasheva A, Zolotova E. Five years' experience with a peripheral veno-arterial ECMO for mechanical bridge to heart transplantation. *J Thorac Dis.* 2019;11(Suppl 6):S889-S901.
3. Lorusso R, Raffa GM, Alenizy K, Sluijpers N, Makhoul M, Brodie D, et al. Structured review of post-cardiotomy extracorporeal membrane oxygenation: part 1-Adult patients. *J Heart Lung Transplant.* 2019;38(11):1125-43.