INTRODUCTION

- Withdrawal of life-sustaining therapy (WLST) is a common cause of death among critically ill patients with subarachnoid hemorrhage (SAH).
- Differences in prognostic evaluations and rates of WLST in SAH clinical trials likely occur.
- Failing to account for the proportion of deaths due to the WLST in SAH clinical trials may:
  1. Introduce bias into trial results
  2. Create a differential and substantial effect on overall survival between study arms
  3. Have significant implications for the interpretation and conclusions of trial results

OBJECTIVES

- **AIM**: To assess the proportion of clinical trials reporting WLST and the potential impact on mortality
- **Primary outcome**: Proportion of trials reporting WLST in subarachnoid hemorrhage clinical trials
- **Secondary outcomes**:
  1. Proportion of deaths secondary to the WLST
  2. Timing of WLST
  3. Factors influencing the decision to withdraw
  4. Potential impact of WLST on trial outcomes
  5. Comparison of trial fragility index and fragility quotient to WLST

RESULTS

- Identification of studies via databases and registers
  - Records identified from: Medline, EMBASE, CINAHL, CENTRAL, Biosys (n = 16,877)
  - Duplicate records removed (n = 3,977)
- Screening
  - Records screened (n = 12,400)
  - Records excluded (n = 12,140)
  - Reports assessed for eligibility (n = 260)
  - Reports excluded:
    - Outside of date criteria (n = 117)
    - Wrong study design (n = 47)
    - Wrong patient population (n = 6)
    - Mortality not reported (n = 29)
- Studies included in review (n = 61)

Figure 1: PRISMA flow diagram

DISCUSSION & CONCLUSIONS

- For the next stage of this research program:
  - Complete Cochrane RoB2 tool for randomized trials
  - Simulation study to evaluate the potential impact of WLST on reported trial outcomes
  - Estimate the degree of fragility in clinical trials
- Future SAH trials should report deaths attributable to WLST and record the justification and timing of WLST to understand the potential impact such decisions have on trial outcomes

ACKNOWLEDGEMENTS

We would like to acknowledge the University of Galway for allowing me to travel to Ireland to present at this international conference.

REFERENCES

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**Primary outcome:** Proportion of trials reporting WLST in subarachnoid hemorrhage clinical trials

**Secondary outcomes**
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METHOD

Search strategy: Medline, EMBASE, CINAHL, CENTRAL, and Biosys from Jan 2001 to Sept 2021, published in top 10 IF journals in general medicine, critical care medicine, neurology/neurosurgery, and neurocritical care

Screening: Studies screened using study title & abstract. Full texts of remaining articles examined using a set of defined inclusion criteria

Inclusions: Critically-ill patients with SAH enrolled in RCTs or controlled studies and mortality reported

Best practice guidelines: Protocol registered with PROSPERO (CRD42021279870), conducted in accordance with Cochrane Handbook for Systematic Reviews of Interventions, and adhered to PRISMA guidelines for reporting
RESULTS

Identification of studies via databases and registers

Records identified from: Medline, EMBASE, CINAHL, CENTRAL, Biosys (n = 16,377)

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Studies included in review (n = 61)

Figure 1: PRISMA flow diagram
RESULTS

- 61 studies (17,888 patients) met inclusion criteria and were included in the analysis
- 30 (49%) were published within the last decade
- Majority (36) of studies were single-center trials
- 36 studies utilized a drug intervention, many of which included simvastatin, magnesium, or clazosentan therapies
- 33 trials had a positive outcome

Figure 2: Interventions in trials
RESULTS

Figure 3. Trials reporting withdrawal of life-sustaining therapies
## RESULTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality in intervention</th>
<th>Mortality in control</th>
<th>WLST #</th>
<th>WLST in intervention</th>
<th>WLST in control</th>
<th>Portion of deaths due to WLST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chou 2008 USA</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>100%</td>
</tr>
<tr>
<td>Diringer 2016 USA</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>Intervention: 100% Control: 0%</td>
</tr>
<tr>
<td>Diringer 2004 USA</td>
<td>34</td>
<td>21</td>
<td>51</td>
<td>32</td>
<td>19</td>
<td>Intervention: 94% Control: 90%</td>
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<tr>
<td>Ironside 2020 USA</td>
<td>7 (2 in hospital)</td>
<td>8 (2 in hospital)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>Intervention: 100% Control: 0%</td>
</tr>
<tr>
<td>Roquilly 2013 France</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>Intervention: 60% Control: 30%</td>
</tr>
<tr>
<td>Tseng 2007 United Kingdom</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

**Table 1.** Studies with WLST reported
RESULTS

1. Timing of withdrawal
   • Not specified, but 1 trial stated most died within 72 hrs and another trial after 48 hrs

2. Factors influencing the decision to withdraw
   • 1 study (of 8 trials that mention WLST) reported 1/3 WLST due to advance directive

3. Justification for withdrawal
   • 1/8 studies: evidence of clinical, TCD and angiographic vasospasm (2/3), and 1 patient had poor neurological function (1/3)
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REFERENCES


CONTACT INFORMATION

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