## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Preventing adverse events during paediatric cancer treatment: protocol for a multi-site hybrid randomised controlled trial of catheter lock solutions (The CLOCK trial) |
| **AUTHORS** | Ullman, Amanda; Takashima, Mari; Gibson, Victoria; Comber, Elouise; Borello, Eloise; Bradford, Natalie; Byrnes, Joshua; Cole, Roni; Eisenstat, David; Henson, Nicole; Howard, Philippa; Irwin, Adam; Keogh, Samantha; Kleidon, Tricia; Martin, Michelle; McCleary, Karen; McLean, Jordana; Moloney, Susan; Monagle, Paul; Moore, Andrew; Newall, Fiona; Noyes, Michelle; Rowan, Gemma; St. John, Amanda; WOOD, ANDREW; Wolf, Joshua; Ware, Robert |

## VERSION 1 – REVIEW

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| **REVIEWER** | Barton, Andrew<br>Frimley Health NHS Foundation Trust |
| **REVIEW RETURNED** | 29-Apr-2024 |

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| **GENERAL COMMENTS** | Brilliant manuscript, very well presented with good evidence. |

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| **REVIEWER** | Kumwenda, Mick<br>Glan Clwyd Hospital, Renal and Diabetes |
| **REVIEW RETURNED** | 30-Apr-2024 |

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| **GENERAL COMMENTS** | I have a few comments and questions, please:<br>1) This is an essential protocol proposal for an RCT comparing T-EDTA and standard catheter locks in preventing CVAD-associated complications, which often cause distressing disruption to the delivery of lifesaving intravenous therapies within paediatric care.<br>2) In their meta-analysis, Takashima and colleagues showed that no catheter locks impacted the prevention and treatment of thrombosis, CVAD failure, and CVAD-associated infection treatment failure. This highlighted the need for high-quality studies, and the choice of T-EDTA for this protocol was innovative.<br>3) Exclusion criteria should include renal failure because of the high risk of E-EDTA toxicity.<br>4) Will the blood samples for culture be taken from peripheral venous access and CVAD lumens? This would assist in diagnosing CABSI.<br>5) Please clarify: Will centres standardise diagnostic tests for CVAD-related thrombosis, such as CT, MRI, ultrasound, and venography? Is radio exposure an issue here?<br>6) Does each centre follow the same guidelines for choosing catheter type, placement, and after-placement to avoid intra-centre variability? For example, different oncologists could have different |

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| | guidelines for their patients, which could, therefore, make data analysis difficult.<br>Many thanks. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1
1) Brilliant manuscript, very well presented with good evidence
a. Author's response: Thank you for your positive feedback.
b. Changes made: No changes.

Reviewer 2
1) This is an essential protocol proposal for an RCT comparing T-EDTA and standard catheter locks in preventing CVAD-associated complications, which often cause distressing disruption to the delivery of lifesaving intravenous therapies within paediatric care.
a. Author's response: Thank you for your acknowledgement of the importance of this work.
b. Changes made: No changes.

2) In their meta-analysis, Takashima and colleagues showed that no catheter locks impacted the prevention and treatment of thrombosis, CVAD failure, and CVAD-associated infection treatment failure. This highlighted the need for high-quality studies, and the choice of T-EDTA for this protocol was innovative.
a. Author's response: Again, thank you. We agree that a catheter lock solution that can target all these complications is required.
b. Changes made: No changes.

3) Exclusion criteria should include renal failure because of the high risk of E-EDTA toxicity.
a. Author's response: Because the solution is only instilled to the length of the catheter with no/ minimal intravascular overflow, the risk for toxicity is low. Therefore, we do not see the requirement of including renal failure as an exclusion criterion. Twice weekly review of the patients by the research nurse will allow for regular monitoring and collection of adverse events.
b. Changes made: No changes.

4) Will the blood samples for culture be taken from peripheral venous access and CVAD lumens? This would assist in diagnosing CABSI.
a. Author's response: Diagnostic investigations (including type and frequency of blood cultures) and treatment of suspected CLABSI will be at the discretion of the clinical team. As per the CDC criteria, DTTP will be used where both peripheral and central cultures are collected. This is outlined in page 19 "Other than CVAD lock solution, all other CVAD insertion, care and management will be in accordance with local clinical practice guidelines (at all study sites)".
b. Changes made: No changes.

5) Please clarify: Will centres standardise diagnostic tests for CVAD-related thrombosis, such as CT, MRI, ultrasound, and venography? Is radio exposure an issue here?
a. Author's response: As above, all diagnostic interventions for suspected thrombosis will be initiated by the clinical teams as per their routine care. This is intended to minimise the research burden for the participants and mimic the clinical settings in which the lock solutions will be used. There will be no research-related radiation exposure in this study. All imaging studies will be performed for routine care at the discretion of the treating clinician.
b. Changes made: No changes.

6) Does each centre follow the same guidelines for choosing catheter type, placement, and after-placement to avoid intra-centre variability? For example, different oncologists could have different guidelines for their patients, which could, therefore, make data analysis difficult.
a. Author's response: All catheter choices and insertion processes are decided clinically for pragmatic reasons. These details are collected – along with type of cancer, infections and treatment protocols e.g., in the electronic case report form (eCRF) to inform analysis. Our statisticians have had extensive experience with clinical trials in vascular access to account for the differences.
b. Changes made: No changes.

## VERSION 2 – REVIEW

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| **REVIEWER** | Kumwenda, Mick<br>Glan Clwyd Hospital, Renal and Diabetes |
| **REVIEW RETURNED** | 31-May-2024 |

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| **GENERAL COMMENTS** | Many thanks for addressing all issues raised. |