Protocol Version Control Log

Version number	Document Date	Submission Date	REC Approval Date	Reason for Change	Summary of Changes
1.2	08/09/2017	21/07/2017	20/10/2017	-	-

Protocol Version Control Log

2.0	27/09/2018	05/10/2018	09/10/2018	Amendment following pilot phase.	Page 2 – Contact details for Nessa Nevels removed in line with staff changes Section 1.5 and section 5- removal of reference to Data Protection Act 1998, insertion of Data Protection Act 2018 Section 2.5 - Addition of section to detail co-enrolment. Section 2.9.1 – Wording added to clarify that intervention period has been truncated to hospital discharge. Section 2.11 – Revised success criteria added. Original success criteria removed Section 3 – Insertion of row in Table 2 to help to identify to sites that a research blood sample should be taken at baseline. Various amendments to clarify data collection from randomisation until hospital discharge and data collection following hospital discharge, including clarity regarding the collection of infection rates. Section 4.1 – Clarification of AE and SAE reporting Section 5.1 – Minor clarifications to data collection processes. Section 7.6 – Update to trial milestones table Section 8.1 – Clarification of site training documentation requirements Section 8.2 – Update to the onsite monitoring schedule
3.0	12/02/2019	08/03/2019	28/03/2019	Addition of secondary	• Section 2.3.1 – addition of secondary endpoint – 'Antibiotic duration for sepsis episode (24-hour time periods from

Protocol Version Control Log

Version number	Document Date	Submission Date	REC Approval Date	Reason for Change	Summary of Changes
				endpoint and clarifications	randomisation)'. Requested following DMC meeting October 2018 by members of DMC and statisticians. • Section 2.9.1 – amendment of wording of protocol advice from 'suggests' to 'supports'. This is primarily for consistence with the wording of the other 2 pieces of advice – was agreed upon by TMG and health psychologists based at WCTU • 2.9.2 – minor grammatical changes • 2.9.2 – clarification added to confirm that off-trial PCT use should not be tested for trial patients from randomisation to 28 days as per the primary objective. • Section 5.1 – clarification of the 28 day follow up mechanisms to expand to include accessing NHS records and contacting the patient themselves or their nominated contact. • Section 9 – removal of reference to Citizen Scientist which no longer exists.

Protocol Version Control Log

4.0	-	-	-	Minor clarifications and addition of telephone consent for Sottish sites. Inclusion of RISC-Sepsis sub-study and COVID-19 sub-analysis.	<u>Protocol</u> • Section 2.3.1 – clarification of secondary endpoint – 'Antibiotic duration for sepsis episode (24-hour time periods from randomisation)' to specify that Daily Defined Dose will be used. • Section 2.4.2 – Additional wording for exclusion criterion 3 to clarify that neutropenia not caused by sepsis would mean a patient is ineligible. • Section 2.7.5 – inclusion of telephone consent option for sites in Scotland in order to bring in line with sites in England, Wales and Northern Ireland telephone consent will aid site staff when obtaining assent from the Guardian/Welfare attorneys during the short 24 hour window. • Section 6.2.2 – Update to the Statistical Analysis Plan section to broaden potential for sensitivity analyses and remove reference to survivor average causal effect (SACE) • Section 6.3 Addition of a sub-group analysis looking at patients with SARS-Cov-2 • Sections 1.5, 2.12 & 6.6 – updates to include the RISC-Sepsis sub-study • Sections 2.7.1, 6.3 and 8 – updates to the protocol to adapt processes following the COVID-19 pandemic • Section 5.6 – clarification of the archiving requirements.

Protocol Version Control Log

Version number	Document Date	Submission Date	REC Approval Date	Reason for Change	Summary of Changes
5.0	10/02/2021	02/02/2021	02/02/2021	Clarification of exclusion criteria including an Urgent Safety Measure to exclude patients in receipt of, or likely to receive, interlukin-6 receptor inhibitor drugs.	• Trial Summary Main exclusions - clarification by addition of one criterion. • Section 2.4.2 - Exclusion criteria – update to wording to include criterion - Any patient given, or anticipated to receive an IL-6 receptor inhibitor drug (e.g. tocilizumab or sarilumab) during their acute hospital admission • Section 2.8.2 - Post-randomisation withdrawals and exclusions reworded with addition of; Patient found to be ineligible post randomisation e.g. patient found to have received more than 24 hours of antibiotics following randomisation, patient identified as requiring long term antibiotics (>21 days), patient received IL-6 blocking drugs prior to randomisation and/or during the intervention period (when biomarkers are being measured).

Protocol Version Control Log

Version number	Document Date	Submission Date	REC Approval Date	Reason for Change	Summary of Changes
6.0	26/10/2021	26/04/2021	14/10/2021	1) Updating trial team contacts 2) removal of project timetable 3) adding clarity around reporting SAEs 4) Updating patient information sheets	Trial contacts updated to include current members of the team Trial summary - removal of project timetable Section 7.6 Removal of reference to study timelines Reporting SAEs - Route of reporting SAEs has been updated from fax to email - SAE form amended to reflect this Monitoring section in protocol updated to remove reference to timeline and be less prescriptive. Section 4.1 Updating the protocol with some clarity added to the adverse event reporting section- suggested changes, (just removed the repeated sections and made it more concise and easy to follow - The patient information sheets have been updated to remove reference to ethnicity data collection as this data is no longer required - it was added as part of the UPH badging the trial received on 19th Oct 2020 and ceased on the 1st June 2021 and because we no longer require this data we have removed this from the information sheets according to GDPR

Protocol Version Control Log

Version number	Document Date	Submission Date	REC Approval Date	Reason for Change	Summary of Changes
7.0	25/11/2021		11/01/2021	To increase volume of blood drawn from participants in RISC-Sepsis sub-study, for optimal analysis of RISC blood samples.	Update to section 2.13, to increase volume of blood when sampling for the RISC-Sepsis sub-study. The increase in volume of blood drawn, only involves patients participating in the RISC-Sepsis sub-study.

Protocol Version Control Log

8.0	22/09/2022	05/10/2022	05/10/22	To provide clarity of post randomisation withdrawals to both the research team and trial management team	Participants may be discontinued from the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they will be followed-up wherever possible and data collected as per the protocol until the end of the trial. Patients may be withdrawn from the trial due to the following criteria:- • Patient and/or Consultee/Guardian/Welfare Attorney withdrawal • Lead Clinician opinion • Following Trial Steering and/or Data Monitoring Committee recommendation for withdrawal of one or more arms of the Trial • Warwick CTU monitor recommendations based on site compliance to the Protocol Following randomisation, a patient may also be withdrawn from the intervention period of the trial (daily blood sampling), and continue to be monitored in trial follow-up, if the local treating clinical and research staff agree that: (b) a patient is identified as requiring long term antibiotics (>21 days) or (c) a patient received IL-6 blocking drugs as part of their emergency care prior to randomisation and/or during the intervention period.

Protocol Version Control Log

Version number	Document Date	Submission Date	REC Approval Date	Reason for Change	Summary of Changes
9.0	20-Mar-2023	23-Mar-2023	n/a	To partially compensate statistically, within financial constraints & study timelines, for higher than anticipated attrition rate in the first 3 days of the sub-study.	This amendment increases the recruitment target of the RISC-Sepsis sub-study of ADAPT-Sepsis to 198 participants in the protocol (from the previous 180 participants). This amendment is to take affect at all ADAPT sites although RISC is only open at a select few.