4th November 2020

Further details of the ADAPT-Sepsis trial can be found at:
https://warwick.ac.uk/fac/sci/med/research/ctu/trials/adaptsepsis/

Dear colleagues,

Thank you for considering taking part in our study following the announcement from the Chief Medical Officer/Deputy Chief Medical Officers on 19th October 2020 to recommend the ADAPT-Sepsis trial as NIHR Urgent Public Health (UPH) research.

On behalf of our Trial Management Group, I would like to take the opportunity to summarise the background to our on-going trial and the basis of UPH badging by the CMOs.

1. Trial aims and funding:
The ADAPT-Sepsis trial was funded as a result of a commissioning brief from NIHR HTA (15/99/02) based on evidence gaps identified by NICE (DG 18) for the treatment of critical ill adult patients with sepsis. The trial was commissioned to address the hypothesis that hospitalised adult patients receiving empiric intravenous antibiotics for suspected sepsis (whatever the infection cause), who are treated using an antibiotic discontinuation protocol based on either plasma C-reactive protein (CRP) or procalcitonin (PCT) daily assays, will have safe decreases in antibiotic treatment duration compared with those treated with standard care alone.

The study is a three-arm randomised controlled trial, where (for the first time internationally) the biomarker results underpinning treatment advice are concealed from treating teams to minimise the risk of bias inherent in these types of decision-support studies.

The study is designed as a superiority trial with a primary clinical effectiveness outcome of total antibiotic days up to day 28 and contains a non-inferiority safety co-primary outcome of all-cause mortality at day 28 (V4.0 study protocol available on our website linked above).

For clarification, our pragmatic trial has adopted the international definition of sepsis (Version 3.0) as the presence of new or worsening organ dysfunction resulting from any suspected or proven infection. Pneumonia is the leading cause of sepsis in the UK including community and hospital acquired bacterial and viral infections.

2. Trial progress:
The trial was initiated in May 2017 with a set-up period followed by an internal pilot at 12 sites. The independent TSC and DMEC approved progression to main trial and this was agreed with NIHR HTA in 2018. Leading up to March 2020, 33 UK recruiting sites (4 nations) had been opened, with another 7 sites in set-up, and 964 patients had participated in the trial.

Due to COVID-19, we decided to pause recruitment to the ADAPT-Sepsis trial at the beginning of March 2020 to allow the critical care national community to focus on other Urgent Public Health research. We have worked to restart ADAPT-Sepsis from August 2020 and have re-opened 19 centres, with 8 having recruiting patients to date, bringing our total patient participation to 1017 at the time of writing.

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NIHR HTA have recently supported an intention to fund trial extension to July 31st 2022 subject to an ongoing Variation to Contract submission and approvals.

3. NICE National Guidance 173 (antibiotic use in COVID-19):
During the 'first wave' of COVID-19 in the UK, it became rapidly apparent that there was widespread use of antibiotics in hospitalised patients with pneumonia presentations and this was most evident for patients with severe COVID-19 requiring critical care where, by definition, they met the sepsis criteria. There was concern at the DHSC that the widespread use of antibiotics may be driving direct patient harm, downstream antimicrobial resistance pressures and diminishing national supplies of important antibiotics that should be reserved for treating bacterial pneumonia/sepsis. NICE rapidly convened to produce national guidance on antibiotic use in COVID-19 (NG 173: published 1st May 2020) aimed at reducing antibiotic exposure and with research recommendations focused on biomarker-guided antibiotic duration decisions and, specifically, that procalcitonin monitoring (thought to be the most promising marker for bacterial infection) **should not** be used in routine care unless as part of a research trial.

In partnership, we have progressed a patient-level review of infection, co-infection and nosocomial infections in critically ill patients (available in pre-print on request) which indicates that, during the 'first wave' in English NHS hospitals, bacterial co-infections at presentation were rare in severe COVID-19, but an overuse of broad-spectrum antibiotics appears to be associated with downstream gram negative nosocomial infections and further sepsis risk in critical care. A related review in Scotland, focused on antibiotic exposure of hospitalised patients with COVID-19, draws similar conclusions (Seaton RA et al. September 2020 Journal of Infection). Notably, Seaton and colleagues identify the impacts of successful antibiotic stewardship for mild-moderate COVID-19 patients managed in ward-based settings but highlight the continuing challenges to guide safe antibiotic stewardship in critical care patients with suspected or proven severe COVID-19.

Therefore, recruitment of COVID-19 patients to ADAPT-Sepsis will help address an area of unmet research need identified by the recent NICE National Guidance during pandemic.

4. Basis for NIHR UPH adoption:
Now that ADAPT-Sepsis has restarted, and with recent reports from PHE that SARS-CoV-2 is becoming endemic in the UK, we have proposed to include COVID-19 patients in critical care who; (i) meet the study eligibility criteria for community acquired sepsis (unchanged from original study) or (ii) meet the study eligibility criteria for nosocomial sepsis (also original inclusion).

The 'second wave' of COVID-19 has commenced in critical care according to national audit data, but it has the potential to be more complex in an autumn/winter setting of mixed viral and bacterial respiratory infections. Therefore, patients with severe pneumonia and sepsis will continue to be exposed to broad range and high potency antibiotics within critical care and there remains a continuing challenge of when to safely discontinue these treatments.

The CRP and PCT biomarker protocol implemented in the ADAPT-Sepsis trial (see study protocol at our website linked above) is based on a wealth of evidence from over 20 years of research in severe

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bacterial, viral and fungal sepsis. The protocol was designed to provide advice to clinical teams on decisions to **stop antibiotics** in adult patients with sepsis and not when to start or re-introduce antibiotics. Based on emerging observational evidence from COVID-19 (NICE NG 173), biomarkers such as PCT and CRP should not be used to make antibiotic initiation decisions for patients with severe pneumonia and sepsis who may require critical care – which is consistent with evidence underpinning our original study protocol. However, our protocol advice thresholds for daily PCT and CRP assays remain relevant to guide decisions to stop antibiotics.

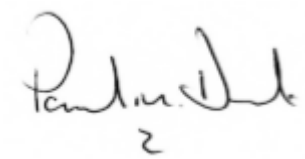
We have agreed a defined secondary analysis for laboratory-proven COVID-19 patients recruited to help provide prospective evidence on biomarker-guided antibiotic treatment decisions in this group. However, our primary aims and analyses remain unchanged for broader pragmatic inclusion of patients meeting the sepsis criteria, receiving antibiotics and admitted to critical care, irrespective of the infection site or pathogen aetiology (the original funded hypothesis). We believe that this will provide the best evidence to inform future NHS clinical practice in critical care as COVID-19 becomes endemic in the UK over the coming period.

To facilitate COVID-19 patient participation in our non-CTIMP trial, we have already agreed study co-enrolment with the main multi-centre UPH studies in severe COVID-19 including RE-MAP CAP, RECOVERY, ISARIC 4C/GenOMICC and RECOVERY-RS.

In summary, we believe that much as been learnt from the first pandemic wave in the UK in critical care which has translated into more lives saved. We now believe that the ADAPT-Sepsis trial has an important role in providing evidence for a more rational and safe use of antibiotic for critically ill adult patients during pandemic and as we move to a new era of endemic COVID-19. We also believe that the benefit of recruiting patients with SARS-CoV-2 pneumonia during the pandemic is not limited to taking the opportunity to inform future stewardship-driven antibiotic prescribing in this infection. Additional value is likely to be gained from providing evidence with broad applicability to other viral pneumonia, such as seasonal flu, which remains an uncertainty in clinical practice that no other trial is likely to be able to address.

Please do not hesitate to contact the trial team and I if you require any further information or clarifications.

Yours faithfully,



Professor Paul Dark
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On behalf of the Trial Management Group

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