Professor Chris BUTLER

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Professor Butler trained in medicine at the University of Cape Town, did doctoral work at The University of Wales College Of Medicine, and studied Clinical Epidemiology at The University of Toronto. He is now a Professorial Fellow at Trinity College, Oxford, and a Professor of Primary Care at the Nuffield Department of Primary Care Health Sciences at the University of Oxford. Professor Butler's main research interests are in common infections (especially the appropriate use of antibiotics and antivirals, diagnostics, and antimicrobial resistance), and health behaviour change (especially motivational interviewing in health care). He has expertise in clinical trials, cohort studies, qualitative research and analysis of routinely collected data. He chairs the Longitude Prize Advisory Panel and is a Fellow of the Academy of Medical Sciences. He was the patient-nominated Royal College of General Practitioners Wales General Practitioner or the Year in 2019, and won the Royal College of GPs Research Paper of the year in 2020. He has published >400 scientific papers. He currently co-leads the UK National Urgent Public Health Priority Platform Randomised Trial of community treatments for Covid-19 (PRINCIPLE: https://www.principletrial.org)

Keynote Lecture IV –

Innovation in design and implementation of primary care clinical trials to generate evidence for community therapeutics for COVID-19: The UK National Urgent Public Health PRINCIPLE Trial example

There were no randomised trials of oseltamivir in the H1N1 pandemic, even though this drug was given out in large quantities, so we will never know if we did more good than harm with that treatment. COVID-19 has demanded the rapid generation and implementation of evidence to better support primary care. Evidence generated during the pandemic in the context where it is to be used is urgently needed, as evidence from hospital trials does not necessarily apply to early treatment in the community, for example. Using traditional approaches, pandemics are often over before relevant trials can be set up, let alone generate evidence to guide care during the pandemic itself. Traditional trial design and implementation takes a long time and is usually limited to the evaluation of a small number of candidate treatments in any one study, and so may not be suited to pandemic circumstances where many candidate interventions may need to be rapidly evaluated and with more interventions emerging subsequent to the start of a trial, thus limiting the changes of enhancing the quality of clinical care during the pandemic itself.

There are few specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective. Most cases are being managed in the community. It is essential that we urgently identify therapeutics that speed recovery and prevent the need for hospital admission. An ideal intervention would be one that is safe, with few side-effects, helps prevent disease progression, and can be administered in the community using existing processes and capability.

This talk covers an example of the rapid initiation and implementation of a novel clinical trial in the community, with findings generated rapidly enough to be implemented during the pandemic itself.

The Platform **R**andomised tr**i**al of treatme**N**ts in the **C**ommunity for ep**I**demic and **P**andemic i**L**ln**E**sses (**PRINCIPLE)** is a multicentre, open-label, multi-arm, response-adaptive platform randomized controlled trial of community treatments for COVID-19.

Innovation in trial design: PRINCIPLE operates under a master protocol that allows the addition of further interventions into the trial while the trial is already in progress, so a new trial does *not* need to be started afresh each time an additional suitable intervention becomes available, and it also means that existing controls can be used efficiently to give rapid answers about the effectiveness of new interventions. Response adaptive randomisation allows the proportion of participants allocated to each intervention to be adjusted, based on emerging data from the trial to increase efficiency and shorten time to results.

Innovation in trial Implementation: We recruit through our traditional route general practice as well as being a paperless 'online' trial, using approaches where the 'patient comes to research' as well as the trial 'taking research to the patient.'

Innovation in the evidence base: Clinical alerts can be sent out to all clinicians in the NHS around the implications of the findings. Readouts for **azithromycin, doxycycline, inhaled budesonide and colchicine** will be presented, with a focus on detailing the benefits from inhaled budesonide treatment.