LESSONS LEARNED REPORT

HTA Reference	16/31/65
Title	Pneumonia Investigation Bundle to Guide Therapy for Hospitalised Community Acquired Pneumonia (PIB CAP Study)
Brief Title	PIB CAP Study
Sponsor	University of Edinburgh and NHS Lothian (ACCORD)
Sponsor's Reference No.	AC18016
Clinical Trials Unit	Edinburgh Clinical Trials Unit (UKCRC Registration no: 15)
Trial Registration	ISRCTN: 42850134 IRAS: 237740
Chief Investigator	Professor Adam Hill
Design	Pragmatic, multicentre, open randomised controlled trial
Primary Objective	To explore whether participants admitted with community acquired pneumonia can safely receive personalised antibiotic therapy within 36 hours of hospital admission
Medical Device	Pneumonia investigation bundle (PIB CAP) uses mRT-PCR assays for 24 respiratory bacteria and viruses and captures most of the aetiological agents in CAP with results available within 6 hours
Comparator	Investigations and treatment per NICE Pneumonia guidelines
Number of participants	843
Grant Start Date	01 December 2017
Proposed End Date	31 March 2022
Study Duration	52 months
HTA Programme Manager	Mark Townsend
Closedown Date	31 March 2021

This report was drafted by Emma Ward (Trial Manager, Edinburgh Clinical Trials Unit, ECTU) and Morag Maclean (Senior Trial Manager, ECTU), reviewed by the Senior Management Teams within ECTU and the Sponsor's office (ACCORD), and approved by Professor Adam Hill (Chief Investigator).

Disclaimer

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STUDY OVERVIEW

The PIB CAP study was established to investigate the use of a pneumonia investigation bundle using fast multiplex real-time Polymerase Chain Reaction assays for 26 respiratory bacteria and viruses along with urine for Legionella Antigen test to personalise antibiotic treatment. This study was led by a multidisciplinary research team based within NHS Lothian and the University of Edinburgh, with co-applicants from Newcastle-upon-Tyne Hospitals NHS Foundation Trust and University of Newcastle, University College London, the University of Southampton and Nottingham University Hospitals NHS Trust. The Edinburgh Clinical Trials Unit (ECTU) were responsible for the operational delivery of PIB CAP including trial management, statistics, data management and health economics. Sponsorship lay with The Academic and Clinical Central Office for Research and Development (ACCORD), a partnership between the University of Edinburgh and NHS Lothian Health Board). A fully specified clinical investigation plan, all patient-facing documentation and a database were finalised and approved. The study was closed on 31 March 2021, 40 months after its official start date and with 25 participants recruited.

Summary of the original PIB CAP Proposal:

Design: Pragmatic, multicentre, open randomised controlled trial

Setting: 5 UK hospitals.

Target population:

- Inclusion criteria: patients ≥16 years old hospitalised with uncomplicated community acquired pneumonia (CAP)+CURB65 score ≥2.
- Exclusion criteria: No capacity to consent; active malignancy; immunodeficiency; solid organ transplant; pulmonary fibrosis; COPD on domiciliary oxygen therapy; mechanical ventilation; end of life care.

Health technology being assessed: Utility of a pneumonia investigation bundle using fast multiplex real-time Polymerase Chain Reaction assays for 26 respiratory bacteria and viruses along with urine for Legionella Antigen test (using BinaxNOW®) to personalise antibiotic treatment. This bundle was called “PIB CAP”.

Control treatment: Investigations and treatment per NICE Pneumonia guidelines.

Planned interventions: Half of the 843 participants were to be randomised to management as per the NICE Pneumonia guideline and half with personalised treatment following PIB CAP investigations (admission throat swab, spontaneous sputum if available and urine for Legionella Antigen test). The group undergoing PIB CAP investigations would have had standard antibiotic treatment as per NICE Pneumonia guideline, but would be personalised following PIB CAP results.

Assessments: Baseline, Day 7 (safety assessment) and Day 30 (assess recovery) and 1 year for health economic analysis. Interventions were to be delivered by the clinical care team supported by the research nurse.

Timetable: 4 months for site training and to finalise approvals; 6 months pilot study; 35 months conducting the study; 6 months data analysis, writing the publication and reports; 1 month close of study and archiving.

Planned recruitment: 5 per calendar month per site.

Primary outcome: Desirability of Outcome Ranking (DOOR) to assess the efficacy and safety of PIB CAP therapy based on assessing (A) day 30 clinical response and (B) day 30 total antibiotics Defined Daily Dose (DDD) to ensure by narrowing antibiotics this does not lead to subsequent additional antibiotic use. What is the probability that a randomly selected participant will have a better DOOR if assigned to receive PIB CAP compared to standard treatment?

Statistical Rationale and Power calculation: A sample size of 358 in each group for 90% power to detect a probability of 0.570 that an observation in the PIB CAP group was more than an observation in the standard care group using a Wilcoxon (Mann- Whitney) rank-sum test with a 5% two-sided significance level. To allow for potential dropouts this sample size was increased to 400 per group [i.e. a 10% drop out rate].To incorporate a design with 4 equally spaced scheduled interim analyses increased the sample size to 843.

Health Economics: A cost-utility (CUA) evaluation using standard NICE reference case specifications. Cost-effectiveness analysis (CEA) of cost per DDD reduction (exposure to antibiotics). Both CUA and CEA was to be assessed by 30 day within trial analysis and longer term economic modelling.

EXECUTIVE SUMMARY

This report will describe the principle causes and contributing factors, as identified by the research and trial management teams, which resulted in the closedown of the PIB CAP study one year before its specified end date. The funder questioned the progress of the study following significant delays during study set-up and the resulting low recruitment number.

Rather than experiencing one single over-riding failure in management or processes, the PIB CAP study had experienced many significant delays that were out of the direct control of the study investigators and unfortunately led to further problems as the study progressed. These issues were accentuated by

staffing changes and capacity concerns, with the study ultimately being terminated early amidst the COVID-19 pandemic.

Attempts were made to adapt the protocol to ensure the study's continuation throughout, and in a realistic setting after, COVID-19. A recovery plan was submitted to the funder that proposed development of the assay to incorporate COVID-19 testing, an extension to study timelines to allow further opportunity for recruitment and the adoption of at least 5 additional sites to aid this recruitment. The plan was not successful as this would have required additional funding for development of the assay which the funder was unable to provide for this type of grant.

The lead research team have learned significant lessons following the events that led to the closure of the study.

FACTORS LEADING TO STUDY CLOSEDOWN AND LESSONS LEARNED

MHRA Categorisation and subsequent impact

The first major source of delay concerned the categorisation of this study by the MHRA as an in vitro diagnostic medical device for performance evaluation (IVD study). This level of complexity had not been factored into the funding application submission. The study grant started on 1st December 2017, with original plans to start the pilot study in April 2018. However, it was not until 1st February 2018 that the sponsor received confirmation that the MHRA categorised this study as an IVD study following extensive discussions between all parties. The IVD categorisation resulted in the study team having to produce a significant amount of extra documentation to meet the regulatory requirements and required requesting specialist SOPs and validation documents from study collaborators in the microbiology laboratories in order to complete the essential document checklist, the investigator brochure, the clinical investigation plan, and the annex VIII statement. All of these documents were reviewed as part of the Sponsor risk assessment within a week of document receipt. However, the risk assessment was not finalised until 13th March 2019, partially due to further discussions with the MHRA regarding pharmacovigilance requirements and delays in receiving additional documentation from manufacturers. At the time of the study start, this was the first IVD for performance evaluation study that had been undertaken by either the Sponsor or ECTU.

Lessons Learned:

1. Careful consideration of the regulatory status of a study before grant submission to ensure all costs and timescales are realistic and have been considered. If there are any changes to the categorisation or significant changes to the design of studies, these would preferably undergo a

repeat funding review and risk assessment to ensure that all of the changes and requirements of the study are met within the funding application.

2. A single point of contact with the MHRA. In this case, the CTU and CI both made contact before the Sponsor ultimately sought clarification.
3. Production of guidance and/or essential document checklists for research teams and manufacturers on what documentation will be required for regulatory submissions and risk assessments.
4. Ideally, the development of a draft protocol at grant application stage, to allow for a clearer understanding of the nature of the study as early as possible for everyone involved.

Site Feasibility and Capacity to Recruit

Despite feasibility questionnaires from two sites being returned with recruitment estimation of 5-10 patients per month this was not achieved due to laboratory availability and capacity, with only one laboratory team member trained in the study and its processes in one instance and clinician availability to confirm eligibility criteria at another. These constraints led to significant under-recruiting.

Lessons Learned:

1. Co-applicants could be asked to be more actively involved in the protocol design to ensure the protocol requirements are deliverable at site.
2. Site feasibility should be tailored to ensure sites are selected that can comply with the requirements of the trial. Robust procedures for checking site feasibility are now in place.
3. Research teams should be encouraged to develop contingency plans from the inception of a study to ensure that other measures, such as opening additional sites, can be taken in the event that a site does not meet the expectations set out in their feasibility questionnaire.

Staff Engagement & Changes

As with all trials, any change in key members of staff is likely to impact on the delivery of the trial and meeting the set milestones. In the PIB CAP trial there were some significant changes.

In summer 2019, the trial manager for PIB CAP resigned and there was an inevitable gap between the incumbent trial manager leaving and the appointment of a new trial manager. Unfortunately, this gap in trial management support coincided with a crucial time for the site set up process leading to delays in this activity. Due to the delays, several sites required refresher training which placed additional burden on trial management, site team and Sponsor resource. This would not have been necessary if the Site Initiation Visits (SIVs) were conducted closer to the time that sites were ready to begin recruitment.

The success of PIB CAP required close engagement with the laboratory staff at recruiting sites who were not always able or have the capacity to engage fully and rapidly provide the documentation required.

Lessons Learned:

1) If HEI recruitment processes allow it would be beneficial to have a rapid method of recruitment of new staff to actively recruiting trials.
2) It would have been better if SIVs were scheduled as close to the issue of Sponsor Authorisation to Open (SATO) as possible to save the need for additional site training and the impact this had on staff resources. The Sponsor SOPs have already been updated with a list of documents that must be in place prior to SIV to prevent these visits from being conducted too early in the site set up process.
3) Identifying a key contact within each site laboratory who would be involved with practical management of the study to secure capacity and confirm the site can maintain study requirements.

Closure of Public Health England Lab (Newcastle)

The Public Health England (PHE) lab in Newcastle that was involved in the initial grant application closed on 1st November 2017 and all the diagnostic work performed by PHE was taken over by Newcastle-upon-Tyne Hospitals NHS Foundation Trust. This transfer led to delays in progressing the site agreement at this key site.

Lessons Learned: As it was a governmental decision to close the PHE lab, there is not much that could have been done to prevent this closure.

Site Withdrawal (Southampton)

Southampton withdrew their participation in PIB CAP due to a concurrently competing recruiting trial. It was hoped that the Southampton site could be replaced but this was not possible.

Lessons Learned: There will always be studies where some sites are not able to take part and drop out. As highlighted previously in reference to site capacity and feasibility, it is especially important to have back-up sites to replace any sites that need to withdraw.

Changes to Antibiotic Prescription Guidelines

During the set up and training conversations with the site in Newcastle, it was noted that the site's practice for antibiotic prescription differed slightly to that of Edinburgh and the standard NICE antibiotic guidelines. As a result, it was necessary to submit a non-substantial amendment to the clinical investigation plan to clarify that the antibiotic prescription table within it was to be used as guidance only and was not prescriptive. Whilst the Newcastle site was technically open to recruitment at this time, the site was not able to actively recruit until the amendment for the change to the clinical investigation plan had been approved.

Lessons Learned: Specific questions around site feasibility should be asked (and a robust process has since been implemented by the Sponsor), and must be completed by sites, during site selection to ensure site have capability and resources to fulfil all the protocol requirements.

Impact of COVID-19

The final and much more recent barrier to the PIB CAP study was the discovery and worldwide spread of COVID-19, which was initially identified in Wuhan at the end of 2019. After being declared a WHO global health emergency, the spread of COVID-19 and its diagnosis in patients in the UK ensured that virology laboratories across the country were, and still are currently, prioritising testing and treatment for this newly discovered coronavirus. At this point 2 sites were open to recruitment but like most research across the UK, recruitment was suspended in March 2020 and recruitment and study activity could not resume until safeguards were in place that could operate alongside government advice. Although it was possible to re-commence recruitment from 1 June 2020 at the Edinburgh site, other NHS R&D departments continued to restrict recruitment to certain research studies and capacity within laboratories UK-wide were still under significant pressure to meet testing demands. Despite the sponsor's introduction of a process for re-starting recruitment to studies during the pandemic, it was quickly realised that this study had to be significantly adapted scientifically to incorporate testing for novel coronavirus into the assay and that it could no longer re-start recruitment using the current version of the protocol.

Lessons Learned: It is difficult to see how this situation could have been managed any differently; however, the study team are mindful that adaptability, where possible, must always be considered in the design and management of clinical research trials. Moreover, the CTU, sponsor, NHS and many other organisations in the world have adapted significantly to a new way of working so if there are future resurgences of COVID-19 or other similar circumstances, studies and sites would be much better equipped to function in such situations.