

Blinded randomised controlled trial of low-dose Adjuvant Steroids in Adults admitted to hospital with Pandemic influenza (ASAP): a trial 'in hibernation', ready for rapid activation

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Scientific summary

Adjuvant Steroids in Adults admitted to hospital with Pandemic influenza

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Scientific summary

Background

The use of corticosteroids in patients with severe sepsis is recommended by international sepsis guidelines. This recommendation is based on evidence from numerous randomised controlled trials and subsequent meta-analyses. In patients who are hospitalised with community-acquired pneumonia, a recent meta-analysis of randomised controlled trials reported a survival benefit from corticosteroid therapy in the subgroup of patients with severe pneumonia. Further large clinical trials are ongoing in the fields of both severe sepsis and community-acquired pneumonia to investigate the role of corticosteroids as adjuvant therapy.

In contrast, there are no completed randomised trials of the use of corticosteroids in patients with pandemic, avian or seasonal influenza infection. Corticosteroid use in influenza is widespread, non-systematic and marked by controversy. A recent meta-analysis of observational studies of adjuvant corticosteroids in influenza found an association with increased mortality but there were important concerns regarding the risks of bias.

Objectives

The aims of the Adjuvant Steroids in Adults with Pandemic influenza (ASAP) trial are to (1) determine whether or not low-dose corticosteroids, given as an adjunct to standard treatment, are beneficial in patients who are admitted to hospital with severe pandemic influenza, and (2) demonstrate that an 'off-the-shelf' model for a trial that is designed, set up and ready to activate during a public health emergency is possible.

Methods

The trial study design and planned analyses are described below. Methodological aspects of trial set-up and delivery that are unique to the 'off-the-shelf' nature of this study are reported in the next section (see *Results*).

This is a pragmatic blinded, randomised placebo-controlled trial to determine whether or not during a pandemic, for adults (≥ 16 years) who are admitted to hospital with an influenza-like illness, a 5-day course of dexamethasone (Dexsol®, Rosemont Pharmaceuticals Ltd) started within 24 hours of admission, in addition to standard care, is associated with a lower risk of death or admission to intensive care than placebo. This trial will be conducted at 30–40 sites across the UK during the first wave of the next influenza pandemic and will recruit 2200 participants, probably over a 6-week period.

Adults with a clinical diagnosis of an influenza-like illness at the time of hospitalisation will be eligible for recruitment to the ASAP trial; a laboratory diagnosis of influenza will not be required. The definition of an influenza-like illness will be confirmed at the start of the pandemic and will conform to the definition provided by Public Health England at the time. Adults who are known to be taking or requiring corticosteroids at the time of hospitalisation, and those who are on medication for the treatment of diabetes mellitus, will not be eligible to participate in the trial.

The study intervention is dexamethasone, administered as an oral liquid preparation, 6 mg once daily for 5 days. Dexamethasone 6 mg is equivalent to prednisolone 40 mg or hydrocortisone 160 mg. The study control is a matching placebo, identical in colour, taste and consistency to the intervention. Participants will be randomised (1 : 1 ratio) to receive dexamethasone or placebo. In addition to the intervention/placebo, all patients will receive standard care for influenza, including oxygen supplementation, fluids, antiviral drugs and antibiotic drugs as appropriate.

In a high-severity pandemic, the primary composite outcome is admission to intensive care or death by day 30. In a low- to moderate-severity pandemic, the primary outcome is time to hospital discharge.

A planned early analysis focused on the primary end points will be performed to provide rapid data to the UK Department of Health prior to the start of the second pandemic wave. Pre-planned subgroup analyses will be conducted for the primary outcome, based on the following baseline factors:

1. duration of symptoms
2. clinical diagnosis of pneumonia
3. underlying comorbid illness
4. severity of influenza.

In parallel with the ASAP trial, we have set up a mechanistic substudy to be conducted at six pre-selected trial-participating sites. The substudy will collect biological samples from 200 ASAP trial participants to determine the interaction of steroid therapy and the host, and to apply this in interpreting the clinical outcomes measured. Two blood samples and one nasal swab for subsequent transcriptomic and microbiological testing will be obtained from participants at baseline and 48 hours post first dose of ASAP trial medication.

Results

This trial has not yet been activated. The status of the trial at the end of the set-up phase is described, together with results from patient and public involvement (PPI) consultation events and hurdles encountered during trial set-up.

Consultations with patients and the public specifically in relation to the consent process for this trial included events with representatives from charitable organisations related to respiratory disorders, PPI representatives of the East Midlands Collaboration for Leadership in Applied Health Research and Care, a library reading group and members of a town council. The majority view from these consultations was a preference for a clear verbal consent process prior to trial enrolment in contrast with a weightier written consent approach; of 42 persons consulted, only two preferred a written consent approach. Initial opinions from a Research Ethics Committee (REC) also favoured a verbal consent approach. However, current legal regulations required a process of written informed consent for this trial.

This trial has been approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) (European Union Drug Regulating Authorities Clinical Trials 2013–001051–12) and the South Central – Oxford C REC (13/SC/0436). Global governance checks have been completed in England, Wales and Scotland, enabling sites to issue local UK NHS permissions. The study is registered, with the International Standard Randomised Controlled Trial Number (ISRCTN) registry and will be conducted in accordance with the principles of the Declaration of Helsinki, the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and UK regulatory and ethical requirements.

Owing to the lengthy hibernation period, MHRA approval was granted on the condition that a substantial amendment is submitted at the time of activation to confirm that there is no change to the risk–benefit analysis of the trial. The requirement for an annual Development Safety Update Report (DSUR) was waived by the MHRA. In place of this, an annual letter will be sent advising of any changes in risk–benefit analysis of the trial until the trial is activated. Standard DSUR submissions will commence once the trial has been activated.

Twenty-nine sites have been granted NHS site permission and a further 11 sites are in the process of obtaining local approvals (data as of 22 January 2015). These sites cover a wide geographical area across the UK, including most major cities. Trial activation will be at the request of the National Institute for Health Research (NIHR). It is anticipated that recruitment will be completed by the end of the first wave of the pandemic.

The biggest challenge in setting up this trial has been the uncertainty regarding the timing and severity of a future influenza pandemic. Hurdles encountered during trial set-up included (1) planning for pandemic-level pressures on NHS resources; (2) agreeing to co-enrolment of patients to other non-interventional cohort pandemic studies; (3) ensuring adequate geographical distribution of participating sites; (4) maintaining engagement with site investigators with respect to a trial that may not be activated for some years; (5) addressing future trial-specific training needs of local investigators; and (6) resilience planning in trial management.

Identified threats to trial delivery include changes to research capabilities or policies during the hibernation phase and lack of staff resources during a pandemic. Timely and sufficient support by Comprehensive Local Research Network units at all participating sites, not least through the redeployment of research staff during the pandemic, will be critical to the successful delivery of this trial.

Conclusions

This is the first multicentre clinical trial that has been set up – to our knowledge – in readiness for rapid activation at the onset of a pandemic. Advance set-up of a pandemic trial with full regulatory approvals in place enables the resolution of many issues at an early stage, outside the ‘heat’ of a pandemic. This study serves as a model for the development of other ‘off-the-shelf’ trials as part of preparedness planning for public health emergencies.

Trial registration

This trial is registered as ISRCTN72331452.

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This report

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