Nottingham University Hospitals NHS
NHS Trust

Early low dose steroids for adults admitted to hospital with influenza-like illness during a pandemic: a randomised placebo controlled trial

ASAP ADJUVANT STEROIDS IN ADULTS WITH PANDEMIC INFLUENZA

CLINICAL TRIAL PROTOCOL

Version: Final Version 3.0 dated 07-Oct-2014

Internal Reference No: 11RM013
Ethics Ref: 13/SC/0436
EudraCT Number: 2013-001051-12
ISRCTN: ISRCTN72331452

Sponsor:	Nottingham University Hospitals NHS Trust
Co-ordinating Centre:	Nottingham Clinical Trials Unit (NCTU)
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Funded by:	NIHR Programme NETSCC Pandemic Flu/ Personal Award Reference Number: 11/46/14
Countries of Recruitment:	United Kingdom

NOTTINGHAM CLINICAL TRIALS UNIT

ADJUVANT STEROIDS IN ADULTS WITH PANDEMIC INFLUENZA

PROTOCOL SIGNATURE PAGE

ASAP Protocol Final Version 3.0 dated 07-Oct-2014

This protocol has been approved by:

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ADJUVANT STEROIDS IN ADULTS WITH PANDEMIC INFLUENZA

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TABLE OF CONTENTS

1 AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Protocol amendment 1 (Amendment ref. SA02)	1.0	23-Oct-13	Dr Wei Shen Lim	Update to consent section; replacement of initial verbal consent with use of a single page combined patient information sheet and consent form at the point of hospital admission.
Protocol Amendment 2 (Amendment ref: SA08)	2.0	11-Feb-14	Dr Wei Shen Lim	Addition of Appendix B (mechanistic sub-study) Correction made to section 6.3.3 that trial treatment will be discontinued if participant is later found to meet exclusion criteria. Added that an appropriately trained research nurse may take written consent. Added that treatment pack will also contain a spoon for drug administration and a wristband for trial participants Minor spelling corrections/administrative changes.

2 SYNOPSIS

Study Title	Early low dose steroids for adults admitted to hospital with influenza-like illness during a pandemic: a randomised placebo-controlled trial
Internal ref. no.	11RM013
Clinical Phase	Phase III
Trial Design	Pragmatic multi-centre double-blind randomised trial
Trial Participants	Adults (≥ 16 years old) hospitalised with an influenza-like illness during a pandemic.
Planned Sample Size	2200 patients. The planned sample size is based on the range of possible scenarios that might be encountered during a pandemic. With 2200 patients, the study will have 90% power to detect a 15% relative reduction in the primary outcome (admission to intensive care or death).
Follow-up duration	Patients will be asked to complete a follow-up questionnaire 30 days after hospital discharge. Completion of the questionnaire is not required for patients hospitalised ≥60 days. Patient outcome information will be collected from hospital-based system records for these patients.
Planned Trial Period	The trial is unique as it will be set up pre-pandemic. Once set-up is complete and all the required approvals have been obtained, the trial will be placed into 'hibernation'. After the initial set-up, there will be 3 distinct phases to the trial. **1) Hibernation phase** During hibernation, regular review (at least annually) of trial procedures and sites will ensure that the trial is maintained in a state in which it can be readily activated to start recruitment in the event of a pandemic. **2) Pre-activation phase** When the National Institute for Health Research (NIHR) decide to activate the trial, a pre-activation phase of four to six weeks will begin immediately. This will include final review of trial procedures, trial drug production and distribution, production and distribution of trial materials and a check of site readiness prior to beginning recruitment. **3) Activation phase** During activation, patients will be recruited into the trial. Recruitment Is planned to be completed within the first pandemic wave, typically of six weeks duration. This phase also includes data collection and follow-up.
Primary Objective	To determine whether during a pandemic, for adults (≥16 years) hospitalised with an influenza-like illness, a 5-day course of dexamethasone started within 24 hours of admission to hospital, in addition to standard care, is associated with a lower risk of death or admission to intensive care compared to placebo.
Secondary Objectives	To determine whether dexamethasone given in addition to standard care is associated with a reduction in the length of hospital stay, the frequency of hospital readmission and/or the frequency of GP consultations after discharge compared to placebo. If dexamethasone is effective, the study will also evaluate its cost-effectiveness.

Primary Endpoint	Admission to intensive care unit or death, within 30 days of hospital admission	
Secondary Endpoints	1. Length of stay in intensive care unit 2. Readmission within 30 days of hospital discharge 3. GP consultations within 30 days of hospital discharge 4. Length of stay in hospital 5. Death within 30 days of admission to hospital 6. Admission to intensive care unit within 30 days of admission to hospital The full statistical analysis plan for this trial includes the flexibility to allow for pandemics of different severity.	
Investigational Medicinal Product	Dexamethasone, given as adjuvant therapy in addition to standard care.	
	Form:	Liquid
	Dose:	6 mg once daily for 5 days from randomisation
	Route:	Oral (or enteral through nasogastric tube)

3 ABBREVIATIONS

AE	Adverse event
ASAP	Adjuvant Steroids in Adults with Pandemic Influenza
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CFR	Case Fatality Ratio
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference of Harmonisation
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ITT	Intention-to-treat
LOS	Length of stay in hospital
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Nottingham Clinical Trials Unit
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NHS	National Health Service
NIHR	National Institute for Health Research
PHE	Public Health England
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMG	Trial Management Group
TSC	Trial Steering Committee
WHO	World Health Organisation

4 BACKGROUND AND RATIONALE

Pandemic influenza occurs when a new influenza A virus strain emerges which is antigenically distinct from circulating influenza strains, and which is able to infect humans, spreading efficiently from person to person causing significant clinical illness in a high proportion of those infected. Since the beginning of the 20th century, there have been 4 influenza pandemics of varying severity. The devastating 1918 pandemic ('Spanish flu') caused by influenza A/H1N1 resulted in 20 to 50 million deaths worldwide, representing a case-fatality ratio (CFR) of 2 – 3%. Subsequent pandemics in 1957 (H2N2) and 1968 (H3N2) resulted in approximately 1 to 4 million deaths worldwide; CFR 0.1 to 0.4%. In contrast, the 2009 pandemic (H1N1) was much less severe. It affected mainly people aged below 55 years of age, and had a low case-fatality ratio (0.025%) in the UK similar to that of recent seasonal influenza viruses [1]. The timing and severity of future influenza pandemics remains unpredictable. There are currently no markers that will predict the pathogenicity or spread of a potential pandemic strain in the human population. Therefore, any plans for a future pandemic need to be flexible and take account of different possible scenarios from mild to severe.

Presentation and prognosis

Influenza virus infection is associated with a wide spectrum of illness, from no symptoms to pneumonia and death. During a pandemic, most people are expected to experience a minor influenza-like illness characterized by fever and cough typically lasting 7 to 10 days. Nevertheless, the UK Pandemic Influenza Preparedness Strategy 2011 recommends that for pandemic planning an estimated 1-4% of symptomatic patients should be expected to require hospital care.[2] Patients may be admitted to hospital either because of influenza-related exacerbations of underlying co-existing illnesses such as chronic obstructive pulmonary disease (COPD), or due to complications of influenza infection such as pneumonia.

Following hospital admission, some patients deteriorate rapidly (within 24 hours) and require intensive care unit (ICU) level support for respiratory failure. The proportion who might require ICU support in a pandemic is difficult to predict, and a range of 15% to 25% of hospitalized patients has been suggested. In a severe pandemic, resource limitations will probably define the upper limit. In the 2009 H1N1 pandemic (a low severity pandemic), 17% of hospitalized patients were admitted to Level 2 or Level 3 care;[3] the median time from symptom onset to ICU admission was 6 days, and from hospital admission to ICU admission was 2 days.

A figure of up to 200,000 additional deaths across the UK over a 15 week period has been proposed for planning purposes in the UK Pandemic Influenza Preparedness Strategy 2011. In the 'low severity' 2009 pandemic, 7% of hospitalized patients with confirmed H1N1 influenza infection died [3] .

Current standard therapy for influenza infection

In the management of patients admitted to hospital with influenza infection during a pandemic, current Clinical Management Guidelines recommend that all adults receive appropriate supportive care, including fluid replacement and oxygen supplementation, and antiviral therapy [4]. In addition, antibiotic therapy is recommended for all hospitalised adults except previously well adults with only influenza-related acute bronchitis.

Corticosteroids in influenza

During the early phase of illness, influenza A virus infection induces inflammatory (e.g. IL-6, IL-8) and T-helper type 1 (Th1) cell immune responses (e.g. IFN-induced protein 10 (IP-10), monokine induced by IFN-gamma (MIG), correlating with clinical illness [5]. Hypercytokinaemia is also recognized in patients with H5N1 influenza infection (e.g. IL-6,IL-10, MIG) with the highest levels found in patients who subsequently die [6]. Similar changes have been observed in patients with 2009 pandemic H1N1 infection [7]. Such inflammatory cytokines may suppress the hypothalamic-pituitary-adrenal axis resulting in relative adrenal insufficiency or compete with intracellular glucocorticoid receptor function, resulting in peripheral tissue steroid resistance [8]. Corticosteroids in low doses (e.g. hydrocortisone ≤ 300mg per day or dexamethasone ≤ 11.25 mg/day) downregulates proinflammatory cytokine transcription and has been shown to improve innate immunity in patients with septic shock [9, 10].

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 [11-14]. During the 2009 pandemic, corticosteroid use in critically ill patients with H1N1 influenza was identified in 83 (30%) of 208 patients in a French registry [15], 107 (44%) of 245 patients in a South Korean cohort study and 126 (57%) of 220 patients in the European Society of Intensive Care Medicine H1N1 registry [16]. The heterogeneity of these cohort studies and non-randomised study designs preclude any firm conclusions regarding the risks or benefits of corticosteroids in influenza. In these cohort studies of critically ill patients with 2009 H1N1 pandemic influenza, the association of corticosteroids with mortality varied from a decrease in mortality, to no effect on mortality or an increase in mortality [13, 15-17]. Some cohort studies observed an association of corticosteroids with an increase in hospital acquired pneumonia, including fungal pneumonia [13, 15-17]. One cohort study of 83 hospitalised patients, of whom 17 received parenteral corticosteroids during the first 72 hours of illness, observed an increased risk of critical illness in corticosteroid treated patients (RR 1.8, 95% CI 1.2 to 2.8) [18]. Although multivariate analyses were employed in most of these studies, bias arising from confounding by indication (corticosteroids prescribed in the sickest patients as a 'treatment of last resort') cannot be fully discounted. The World Health Organisation (WHO) Clinical management of human infection with pandemic (H1N1) 2009 : revised guidance[19] recommended that systemic corticosteroids should not be given in severe influenza unless indicated for other reasons or as part of an approved research protocol. A Cochrane meta-analysis of studies of corticosteroids in influenza is on-going and will inform the yearly review of the Trial Protocol during the hibernation phase.

A) ***Effectiveness of corticosteroids in pneumonia.*** Trials of corticosteroids in patients hospitalised with community acquired pneumonia have reported varying results. Meijvis *et al* (n=304) observed a significant reduction in median length of stay together with greater declines in C-reactive protein (CRP) and interleukin-6 levels in the treatment arm (dexamethasone 5 mg for 4 days) [20]. In contrast, Snijders *et al* (n=213) did not detect a significant difference in clinical cure rate at Day 7 despite a faster rate of defervescence and decline in CRP levels in the treatment arm (prednisolone 40 mg for 7 days) [21]. An earlier small, inadequately powered, open-labelled trial by Mikami *et al* (n=31), did not detect any statistical difference in length of stay between groups [22].

In patients with severe community acquired pneumonia admitted to intensive care (ICU) [23], Confalonieri *et al* found hydrocortisone was significantly associated with improved oxygenation and a reduction in multiple organ dysfunction score on Day 8, and a reduction in delayed septic shock. This trial was stopped early (n=46) per protocol after the upper stopping boundary for improvement in oxygenation (PaO_2/FiO_2 ratio) was achieved. A significant reduction in length of stay (13 v 21 days, p = 0.03) and mortality (0% v 30%, p=0.009) was also observed.

B) Effectiveness of corticosteroids in sepsis. A systematic review of trials examining the benefit of corticosteroids in severe sepsis and septic shock in adults identified [24] 12 randomized or quasi randomised trials (n=1228) comparing low dose corticosteroids (hydrocortisone ≤ 300mg per day (equivalent to dexamethasone 11.25 ≤ mg/day)) for ≥ 5 days with placebo or supportive care. The 28-day mortality for treated versus control patients was 37.5% versus 44.1% (RR 0.84, 95% CI 0.72 to 0.97). These results included the study by Confalonieri *et al*, 2005. Similar results were observed when this trial was removed from the analysis (RR 0.87, 95% CI 0.77 to 0.98). These studies of corticosteroids in sepsis differ from the studies in community acquired pneumonia in the timing of corticosteroid intervention; occurring later in the disease process when severe sepsis or septic shock was evident.

Potential harm of corticosteroids

A systematic review of corticosteroid trials in severe sepsis and septic shock did not identify any increased risk of gastroduodenal bleeding, superinfection or neuromuscular weakness. An association with an increased risk of hyperglycaemia (RR 1.16, 95% CI 1.07 to 1.25) and hypernatraemia (RR 1.61, 95% CI 1.26 to 2.06) was noted.

Of trials in community acquired pneumonia, Meijvis et al observed that hyperglycaemia was commoner in the treatment group, while Snijders *et al* noted that the risk of hyperglycaemia requiring additional therapy was non-significantly higher in the treatment group (2.3% of 104 v 0.9% of 109, p=0.27) [20, 21]. Snijders et al observed an increase in late failures in corticosteroid treated patients compared to controls; described as the need for an additional course of antibiotics, need for another or prolonged course of prednisolone or development of a parapneumonic effusion necessitating additional therapy. Rebound inflammation due to the withdrawal of corticosteroids may explain this finding. In contrast, Meijvis *et al,* did

not observe any differences in late failure. This may relate to relative differences between the half-lives of the different corticosteroids tested (prednisolone vs dexamethasone).

A meta-analysis of trials investigating the use of corticosteroids in acute bacterial meningitis observed that participants treated with corticosteroids had an increase in recurrent fever (RR 1.27, 95% CI 1.09 to 1.47) [25]. The rate of persistent fever was lower in the corticosteroids treated patients (RR 0.29, 95% CI 0.12 to 0.70) while other complications (including gastrointestinal haemorrhage) occurred in similar proportions of treatment and control groups.

Choice of trial intervention

Dexamethasone, compared to prednisolone, has a) minimal mineralocorticoid activity and does not affect sodium and water balance, thus avoiding potential problems with fluid retention which are not uncommon in severe viral pneumonitis, and b) a comparatively long biological half-life of 36 to 54 hours; thus extending the pharmacological effects of a 5 day treatment course to over 11 days and potentially offering protection against late failures due to rebound inflammation.

Description of study intervention

The study intervention is dexamethasone administered as an oral liquid preparation, within 24 hours of hospital admission. The regimen is 6 mg once daily for five days. Dexamethasone 6 mg is equivalent to prednisolone 40 mg or hydrocortisone 160 mg.

The oral liquid preparation will enable the vast majority of eligible participants to receive the intervention except those who are either strictly 'nil by mouth' or are unable to swallow. For some of these participants, administration via an enteral feeding tube will be possible. This approach is similar to the manner in which oseltamivir (no IV formulation licensed at the time) was administrated during the 2009 pandemic, when only a small proportion (less than 3%([26], [27])) of patients in intensive care received 'off-licence' intravenous antiviral therapy.

5 OBJECTIVES

5.1 Primary Objective

To determine whether during a pandemic, for adults (≥16 years) hospitalised with an influenza-like illness, a 5-day course of dexamethasone started within 24 hours of admission to hospital, in addition to standard care, is associated with a lower risk of death or admission to intensive care compared to placebo.

5.2 Secondary Objectives

To determine whether dexamethasone given in addition to standard care is associated with a reduction in the length of hospital stay, the frequency of hospital readmission and/or the frequency of GP consultations after discharge compared to placebo. If dexamethasone is effective, the study will also evaluate its cost-effectiveness.

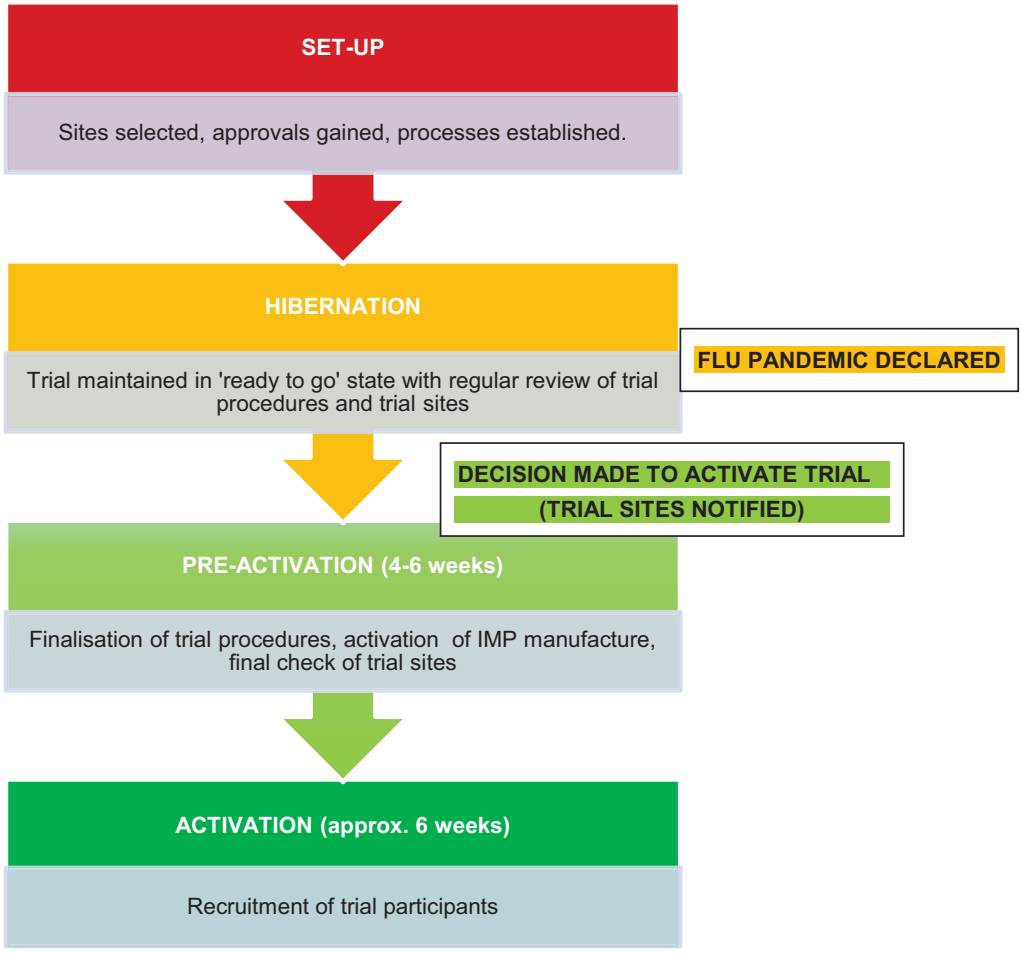
6 TRIAL DESIGN

6.1 Summary of Trial Design

The ASAP trial is a **pragmatic multi-centre double-blind randomised placebo-controlled trial.** The trial design is based on the event of a high-severity pandemic; this being the default position at the start of a pandemic when the severity of a pandemic may not yet be apparent.

The trial will be set-up pre-pandemic. Once set-up is complete and the required approvals have been obtained, the trial will be placed into 'hibernation'. It will be activated during an influenza pandemic only if instructed by the National Institute for Health Research (NIHR). During the hibernation phase, regular review (at least annually) of trial procedures and sites will ensure that the trial is maintained in a state in which it can be rapidly activated to start recruitment in the event of a pandemic. If the NIHR activate the trial it will move to a pre-activation phase of 4-6 weeks. This final phase of trial set-up will include production and distribution of the trial drug and trial materials, finalisation of trial procedures, and a check of site readiness prior to beginning recruitment. A summary of the trial phases is shown in Figure 1.

Figure 1: Phases of ASAP trial



Based on a high-severity pandemic the trial will recruit 2200 patients, and flexibility has been included in the design of this trial to allow for pandemics of lower severity. Detailed information can be found in the Statistical Analysis Plan. The final sample size will be determined in conjunction with the Trial Steering Committee during the activation phase of the trial, once information about the severity of the pandemic is available. It is anticipated that there will be up to 50 centres participating in the UK, covering a wide geographical spread.

Adults (≥16 years) admitted to hospital with an influenza-like illness will be screened for entry into the trial within 24 hours of admission to hospital. Once consent for trial participation has been obtained, eligible patients will be randomised into the trial. Participants will be allocated to receive either dexamethasone or placebo. Both will be given as a liquid (orally or via a nasogastric feeding tube) once a day for 5 days whilst the participant is in hospital, or continued at home if the participant is discharged within 5 days of admission to hospital. All other clinical care will be according to national clinical management guidelines for pandemic influenza.

Routinely available data recorded in hospital records at the time of hospital admission will be collected once consent for trial participation has been obtained. Data on outcome will be collected from hospital

records upon discharge from hospital, or on Day 30 whichever is sooner (Day 1 = day of admission to hospital).

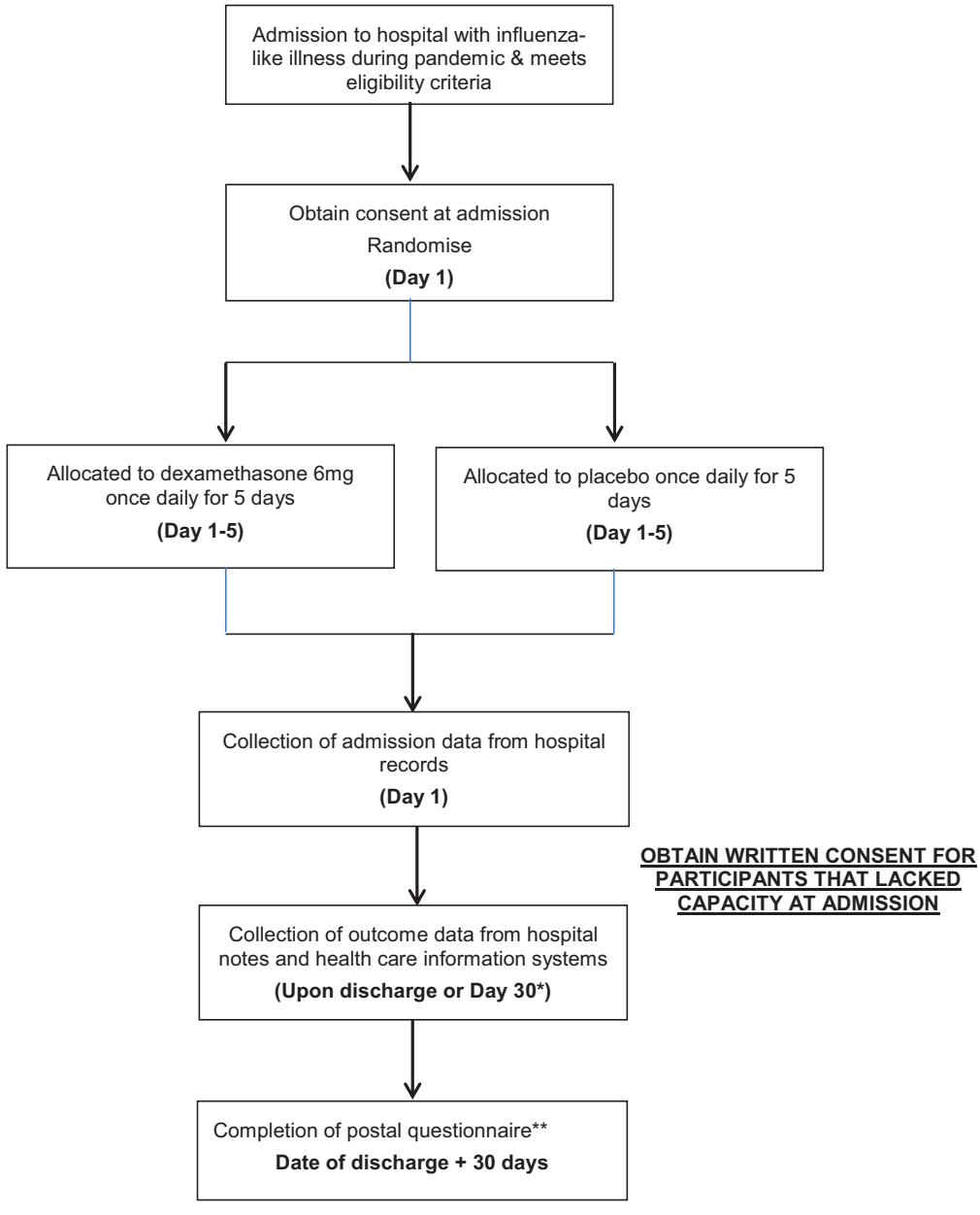
Participants will be sent a postal follow-up questionnaire to complete 30 days after hospital discharge. This will ask whether they have consulted their GP or been readmitted to hospital since being discharged from hospital. In addition, for those who were discharged within 5 days of admission and given their trial treatment to take home, information about treatment compliance will be requested. Participants who do not return this follow-up questionnaire within seven days of the expected completion date will be contacted by telephone by a member of the Nottingham Clinical Trials Unit (NCTU) to request the information. If a participant remains hospitalised at Day 60, completion of the follow-up questionnaire is not required. Patient outcome data for these patients will be collected from hospital-based system records.

Participants do not have any additional study visits.

Participants are considered to be in the trial once the trial treatment pack label has been completed (randomisation) until the follow-up questionnaire has been received by the NCTU (or, when a participant, who fails to return the questionnaire, provides the answers over the telephone instead). For any participants that die, inclusion in the trial will be from randomisation until the date of the participant's death. The participant will be considered lost to follow-up if the questionnaire is not returned and the NCTU are unable to contact the participant by telephone.

Please see Figure 2 for an overview of the trial design.

Figure 2: Overview of trial design



*Data collected at discharge or Day 30 if the patient remains hospitalised, whichever is sooner. In event of death data will also be collected.

** For patients hospitalised ≥60 days, no follow-up questionnaire is required; patient outcome data will be collected from hospital-based systems

6.2 Outcome measures

6.2.1 Primary outcome

Admission to intensive care unit or death, within 30 days of admission to hospital.

6.2.2 Secondary outcomes

1. Length of stay in intensive care unit
2. Readmission to hospital within 30 days of hospital discharge
3. GP consultations within 30 days of hospital discharge
4. Length of stay in hospital
5. Death within 30 days of admission to hospital
6. Admission to intensive care unit within 30 days of admission to hospital

The design and analysis of the trial includes the flexibility to allow for pandemics of different severity. The outcome measures described in this section relate to a high-severity pandemic. Further information on the outcome measures, including those for a pandemic of low/moderate severity, can be found in section 9.

6.3 Trial Participants

6.3.1 Overall Description of Trial Participants

Adults (≥16 years) admitted to hospital with a clinical diagnosis of an influenza-like illness during a pandemic.

6.3.2 Inclusion Criteria

During an influenza pandemic, patients are eligible for entry into the trial if they:

- are ≥ 16 years of age
- have been admitted to hospital within the previous 24 hours with a clinical diagnosis of an influenza-like illness
- have given consent (see section 6.4.2)

6.3.3 Exclusion Criteria

Patients are not eligible for the trial if **ANY** of the following apply at the time of admission to hospital:

- known to be taking oral or IV corticosteroid treatment
- require treatment with oral or intravenous corticosteroids upon admission to hospital as standard treatment for comorbid illness
- known to be on insulin or oral medication for the treatment of diabetes mellitus
- known contra-indication to dexamethasone or any of the excipients (please refer to current version of SPC)

Where a patient is entered into the trial and later found to meet any of the exclusion criteria detailed above, continuation of trial treatment will be discontinued. Data will continue to be collected unless the participant specifically withdraws their consent to this. Please see section 7.5 for further information.

6.4 Study Procedures

A summary and timing of the study procedures is shown in Table 1.

Table 1: Study procedures and data collection in the ASAP trial

Assessments	Day 1 Screening and enrolment	Day 2	Day 3	Day 4	Day 5	Hospital discharge/ Day 30*	Hospital discharge + 30 days
Screen for eligibility	X						
Obtain written consent	X						
Randomise	X						
Complete hospital admission information	X						
Administer trial treatment	X	X	X	X	X		
Obtain written consent# for patients that lacked capacity at enrolment		X#	X#	X#	X#	X#	
Collection of primary and secondary outcome data from hospital notes*						X	
Collect follow-up outcomes from postal questionnaire							X**
Serious Adverse Event	Collect from randomisation throughout trial. See section 8 for information on safety reporting requirements.						

* Data collected at hospital discharge when the discharge is less than 30 days since admission. Data collected at Day 30 if the participant is still in hospital at Day 30.

** Not required if participant is hospitalised ≥ 60 days.

This applies ONLY to those participants that lacked capacity to consent at enrolment. For these participants, written consent must be sought as soon as practicable following the emergency treatment and prior to the patient being discharged from hospital

6.4.1 Screening and Eligibility Assessment

During a pandemic, adults (≥16 years) admitted to hospital with a clinical diagnosis of an influenza-like illness and who meet the trial inclusion criteria will be identified by the clinical admitting team. Clinical nurses who admit patients with influenza will be trained to provide information about the trial to patients and their families.

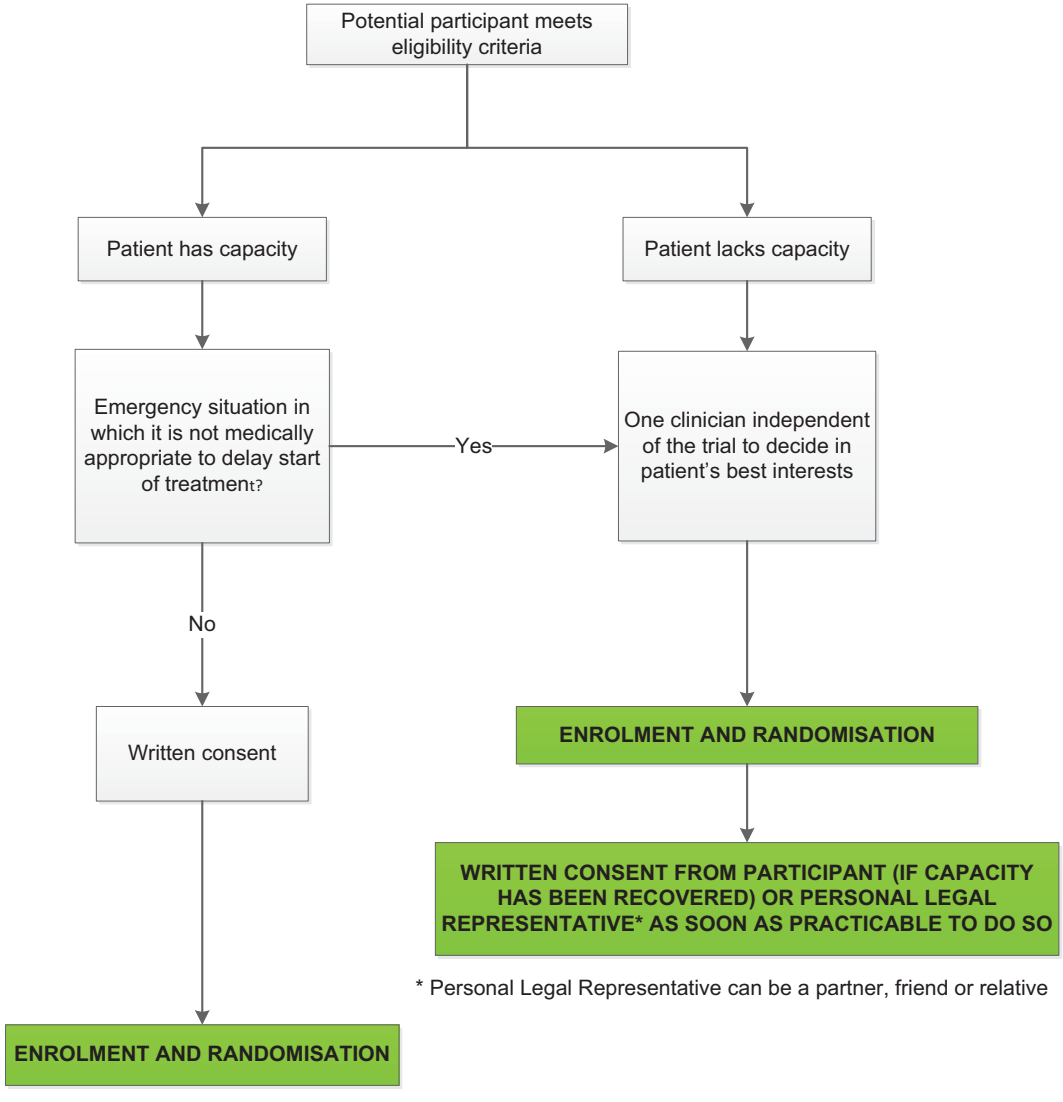
Pre-prepared advertising material approved by the relevant ethics committee will be used during the activation phase to raise public awareness of the trial.

6.4.2 Consent

The challenges of obtaining consent for a trial of an acute intervention in an emergency setting within the context of a pandemic are recognised.

Severe pandemic influenza constitutes a medical emergency; these patients can deteriorate rapidly and dramatically – the average time from hospital admission to ICU admission was 1 day in the 2009 pandemic. In addition, the context of a pandemic means that acute health care resources will be exceptionally stretched, through a combination of high healthcare demand and high levels of staff sickness. These challenges to the clinical service will also impact significantly on research delivery. Recruitment to the ASAP trial must not result in any significant delay to patient care, either to the potential participant or to other patients not being approached about the trial. Therefore consent for trial participation needs to be integrated into routine clinical care during a pandemic. This means approaching patients and their families whilst they are being assessed and triaged at hospital admission, and offering participation in a way that minimises disruption to patient care. Thus written consent for the trial will be obtained from potential participants using a short, single page combined information sheet and consent form at hospital admission points (see Figure 3). A full information leaflet will also be given to participants to read at a later time.

Figure 3: Procedure for obtaining consent for the ASAP trial



6.4.2.1 Patients with capacity to consent (non-emergency situation)

During a pandemic the health service will be in crisis, and triage of patients with influenza-like illness at hospital admission will mean there will be limited time in which to obtain consent from patients. Thus potential participants will have a brief explanation of the trial and be provided with brief written information about the trial in the form of a single page combined information sheet and consent form. After the trial explanation they will be asked if they are willing to be recruited. If they say yes they will be asked to sign the consent form section on the patient information sheet.

Specifically, the responsible doctor or an appropriately trained nurse will explain to the patient that they will receive the usual care for influenza but that in addition to this, they can be enrolled in a research study that aims to improve the treatment of patients with influenza during a pandemic. It will be explained that the study is being undertaken to see whether using a steroid drug called dexamethasone will help patients with influenza infection by reducing the number of patients who have severe outcomes (such as death or admission to intensive care) or by shortening length of stay in hospital. The doctor or an appropriately trained nurse will explain that, in some studies, dexamethasone has been shown to improve outcome for patients with pneumonia or severe 'blood poisoning', and that whilst we hope it will also improve recovery after influenza infection, at present we cannot be sure about this. It will also be explained that if they agree to take part in the study, they will be given a liquid solution once a day for 5 days of either dexamethasone or placebo orally, or if medicines cannot be taken orally, via a feeding tube. Also, they will be sent a short postal questionnaire to complete.

The patient information sheet and consent form will be produced in triplicate copy format; 1 copy for the participant, 1 copy for the patient's medical notes and 1 copy for the Investigator Site File.

The patient will also be given a full information leaflet to keep, which will explain that they can withdraw from the trial at any stage, if they wish.

Once written consent has been given, the patient will be randomised (see section 6.4.3) and trial treatment commenced.

6.4.2.2 Patient with capacity to consent (emergency situation)

Where a patient has capacity to consent but is in an emergency situation whereby it is not medically appropriate to delay the start of treatment, **one independent doctor** should consider the patient's eligibility criteria and any known views of the patient about trial participation and decide whether or not to enroll the patient into the trial.

Once the decision has been made to enter the patient into the trial this must be documented by the clinician in the patient's medical notes. The participant may then be randomised and trial treatment commenced. Written consent must be sought later (see section 6.4.2.4)

6.4.2.3 Patients without capacity to consent

Patients admitted to hospital with influenza may have impaired consciousness, may be confused, or may have an underlying condition such as dementia that impairs their capacity to give properly informed consent. In accordance with the regulations concerning emergency situations where the treatment to be given as part of the trial needs to be given urgently and time does not allow for consent to be obtained, incapacitated patients may be entered into the trial.

Lack of capacity should be determined by the patient's attending clinician.

If the patient lacks capacity to give meaningful consent **one independent doctor** should consider the patient's eligibility criteria and any known views of the patient about trial participation and decide whether or not to enroll the patient into the trial.

The consent decision must be documented in the patient's medical notes.

Once consent has been given, the participant will be randomised and trial treatment commenced. Written consent must be sought later (see section 6.4.2.4)

6.4.2.4 Written consent for patients that lacked capacity at enrolment and emergency situations

For patients that lack capacity to consent at enrolment or patients with capacity that are entered into the trial under emergency situation regulations, written consent must be obtained by a doctor or appropriately trained nurse from the participant (if capacity has been recovered) or Personal Legal Representative as soon as it is practicable to do so.

A Personal Legal Representative may be a partner, friend or relative.

The participant's decision to withdraw would overrule any decision made by a doctor or Personal Legal Representative.

6.4.3 Randomisation

Batches of treatment packs will be supplied directly to trial sites from one or more manufacturing units. Each batch will contain a number of sealed treatment packs in a consecutively numbered series.

The following will be included in the treatment pack:

- A 75ml bottle of either dexamethasone 2mg/5ml or placebo (sufficient for 5 days of treatment)
- Instructions for the take home pack (for participants discharged within 5 days of admission)
- Administration instructions
- A spoon for drug administration
- A trial wristband to enable identification of trial participants during hospital transfers

Trial treatment packs will be available in each area where patients with influenza will be admitted during a pandemic. The two treatments, dexamethasone and placebo, will be indistinguishable. Each treatment pack will be labelled with the trial name and a unique identification number. This will be the Participant's ID Number. NCTU will generate and hold the randomisation sequence according to their SOP.

Once consent for trial participation has been obtained, allocation to trial treatment will be by taking the next in the series of treatment packs at that area each participating site. The trial pack label will be completed and the trial treatment prescribed.

Treatment will be administered as soon as possible, as an addition to standard care.

Participants will be considered to be in the trial once the pack label has been completed regardless of whether or not they take any allocated treatment.

Packs which have been tampered with will be removed from the trial, and any packs used out of sequence will be investigated to ascertain why this happened and whether there was any potential for bias.
The following steps will be taken to guard against participants being randomised into the study more than once:

- Site staff obtaining consent from trial participants at hospital admission points will be trained to ask patients if they have previously participated in the study.
- Reminders of the need to check with patients about previous participation in the study will be in place for clinical staff at hospital admission points.

However given the mechanism of randomisation and the circumstances in a pandemic, it is not possible to completely remove the possibility that someone could be randomised more than once. The analytical approach to deal with this is described in section 9.1.

6.4.4 Collection of hospital admission data

Once consent has been obtained, routinely available data recorded in hospital notes at the time of hospital admission will be recorded on the Case Report Form (CRF) by site staff. This will include patient contact details, patient demographics, time of onset of symptoms, prior treatment, routinely collected clinical observations and test results.

6.4.5 Subsequent assessments

Participants will not have any additional study visits. Data will be collected as follows:

Hospital discharge or Day 30

At hospital discharge, or Day 30 if the participant remains in hospital, outcome data will be collected from the medical notes by research staff at site and recorded on the CRF. This will include patient discharge status, critical care admission, in-hospital treatments including IMP compliance and relevant routinely obtained microbiological test results.

A regular check of hospital systems will need to be performed by site staff to ascertain patient status, including outcome information for those patients hospitalised ≥60 days.

Follow-up

Participants will be asked to complete a postal follow-up questionnaire 30 days after being discharged from hospital. For any participant who remains hospitalised at Day 60 no follow-up questionnaire is required.

The questionnaire will ask about any GP consultations or hospital readmissions within 30 days of discharge from hospital. In addition, for participants who are discharged within 5 days of admission and given their trial treatment to take home, information about treatment compliance will also be requested. The questionnaire will be posted from the NCTU to trial participants, with a prepaid and addressed envelope to return to the NCTU.

Any participants who do not return the questionnaire within 14 days of the due date for completion will be contacted by telephone by the NCTU. The participant will be considered lost to follow-up if the questionnaire is not returned, and they have either not been contactable by telephone or have declined to complete the questionnaire by telephone.

Identifiable data will be collected for the purpose of the follow-up and the patient's details will be registered with the Health and Social Care Information Centre (HSCIC) to find out how they are doing after they have left hospital.

6.4.6 Maintenance of randomisation codes and procedures for unblinding

Clinicians, participants and outcome assessors (research team) will be blinded to the treatment allocation.

The randomisation schedule will be stored centrally on a restricted area of the university's network storage. Access will be restricted to the IT team at the NCTU and central university Information Services' support staff. The research team will not have access to this.

In general there should be no need to unblind the allocated treatment. If a contra-indication to dexamethasone develops after randomisation (e.g. evidence of severe drug reaction), the trial treatment should simply be stopped. Unblinding should happen only in those rare cases where the doctor believes that clinical management depends importantly upon knowledge of whether the participant received dexamethasone or placebo. In those few cases where urgent unblinding is considered necessary, the date and reason for breaking the code will be recorded. It is recommended that any decision to unblind is discussed with the coordinating centre prior to this being done.

An emergency 24 hour trial contact number for unblinding purposes will be supplied to trial sites upon activation of the trial.

6.5 Definition of End of Trial

The end of trial is the date of receipt of the last follow-up information (questionnaire or, for any patient hospitalised more than 60 days, the date of obtaining patient outcome data from hospital-based system records).

6.6 Discontinuation of trial treatment or withdrawal of participants

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue study treatment at any time if they consider it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at enrolment)
- Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Consent withdrawn

6.6.1 Discontinuation of trial treatment

A participant may discontinue treatment either at their own request, or if it is felt in their best interest by the attending clinician. A participant who discontinues treatment (for whatever reason) will remain in the trial for the purpose of collection of follow-up data, unless they have specifically requested withdrawal from further follow-up (see section 6.6.2).

Each participant has the right to discontinue trial treatment at any time. If this happens, they will receive standard care. Participant's data will be analysed in their allocated group as "intention to treat" regardless of whether or not they received the intervention.

6.6.2 Withdrawal from the trial

Each participant has the right to withdraw from the study at any time. For those participants without capacity to consent to the trial at the time of admission and who were consented by a legal representative, withdrawal from the trial may either be at the participant's own request (if they regain capacity) or at the request of their relative /legal representative. The participant and the relative/legal representative will be made aware that this will not affect the participant's future care.

The reasons for leaving the study will be requested and recorded, but participants are not obliged to give reasons. Participants will be assured that withdrawal will not affect the future care they receive. They will be informed that data collected up to the point of withdrawal will be retained and may be used in the final analysis and that their NHS number will be registered with the Health and Social Care Information Centre (HSCIC) to follow them up after they leave hospital (unless specifically requested not to do so), but they will not be directly contacted for the purpose of obtaining follow-up information.. There will be no replacement of participants who withdraw.

6.7 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records and clinical charts.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). In this trial the follow-up questionnaire will be used as the source document for obtaining information about secondary outcome measures (re-admission to hospital and/or consultation of GP within 30 days of hospital discharge).

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent document, the participant will be referred to by the unique participant ID number, not by name.

7 TREATMENT OF TRIAL PARTICIPANTS

7.1 Description and manufacture of trial treatment

Intervention: Dexamethasone 6 mg as a liquid solution (15ml) once daily for 5 days, administered orally or via enteral feeding tube.

Control: Matched placebo solution (15ml) once daily for 5 days, administered orally or via enteral feeding tube.

Dexsol (Dexamethasone) 2mg/5ml Oral Solution manufactured by Rosemont Pharmaceuticals Ltd (PL 00427/0137) will be used in this trial. Rosemont will also manufacture a matching placebo formulation.

Inactive ingredients in the trial treatment (active and placebo): Benzoic acid, propylene glycol, citric acid monohydrate, liquid maltitol, garden mint flavour (containing isopropanol and propylene glycol), liquid sorbitol non-crystallising, sodium citrate and purified water.

7.1.1 Dosage

Participants will receive 15ml dexamethasone (6 mg) or placebo as a liquid solution once daily for 5 days, administered orally or via a nasogastric feeding tube.

All other care will be according to national clinical management guidelines for pandemic influenza

First dose of IMP
The first dose of IMP should be given as soon as possible after consent for trial participation has been obtained, regardless of the time of day.

Subsequent doses of IMP
The date when the first dose of IMP is given to the trial participant should be considered as Day 1 of IMP treatment regardless of the time the dose was given. The second dose of IMP should not be given until the following day (Day 2), preferably in the morning. Further doses should ideally be given each morning.

Please note that this means for any patient receiving their first dose of IMP in the early hours of the morning (Day 1), the dose interval between first and second dose will be more than 24 hours. For those patients randomised late evening, the second dose will be given the following morning and thus the dose interval will be shorter, however this is not expected to be less than 8 hours.

7.1.2 Packaging and Labelling

Rosemont will ship bulk supply of dexamethasone and placebo to one or more manufacturing units, who will be set up to provide the randomised final labelling, packaging and release service in order to ensure the short timeline from activation to the start of trial recruitment is met.

The manufacturing units will receive bulk active and placebo bottles from Rosemont. They will over-label a single 75ml bottle according to Annex 13 and pack with written instructions in a clear outer pack so that the primary packaging label can be read through the pack.

The final product will be QP released by the designated person at the manufacturing unit.

An outer dispenser pack will be assembled containing, in number order the finished active and placebo packs. This will allow the trial treatment packs to be removed from the dispenser in sequence order.

The manufacturing unit where the packaging and release occurs will distribute trial supplies to participating sites.

7.2 Storage of Trial Treatment

The trial treatment will be received and stored by the main pharmacy at each hospital for distribution to the point(s) of patient admission within the hospital. Each participating site main hospital pharmacy will take receipt of numbered supplies from one of the manufacturing units.

Trial treatments will be stored at room temperature below 30 ºC. In the local pharmacy, all trial treatments should be stored in a secure location. The main hospital pharmacy will supply batches of individual participant packs to Admission Points: areas within their hospital where influenza admissions occur.

7.3 Compliance with Trial Treatment

Compliance with trial treatment for hospitalised participants will be assessed from their medication chart which nursing staff will complete. This information will be collected and recorded on the CRF. If the

participant is discharged before 5 days, they will be instructed to complete their trial treatment at home. Compliance with study medication following discharge will be obtained from information requested in the follow-up postal questionnaire.

Compliance with trial treatment is expected to be good.

7.4 Accountability of the Trial Treatment

The participant packs of trial treatment will be supplied by the manufacturing units to the main hospital pharmacy at participating sites. All movements of study medication between the manufacturing units and main hospital pharmacies will be documented. The main hospital pharmacies will record the distribution of all trial medication to the admission points within the hospital.

An accountability log will be maintained at each admission point within the hospital and will be completed upon allocation of trial treatment pack to a participant. Completed accountability logs will be returned to the main hospital pharmacy.

Unused participant packs will be retrieved and accountability completed, before local destruction.

7.5 Concomitant Medication

Throughout the trial investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the exclusion criteria (see section 6.3.3). If these are required during the five days of IMP administration, the participant will be withdrawn from the trial treatment.

The following specific medications, other than the trial treatment, taken during the study will be recorded in the CRF:

a) antiviral drugs
b) antibiotics
c) corticosteroids given after completion of trial treatment

8 SAFETY REPORTING

The definition of a serious adverse event (SAE) is problematic in the context of the ASAP trial since participants are likely to be critically ill patients and progression of pandemic influenza can lead to significantly life threatening and serious conditions, which are outcomes for this trial.

Events that are part of the natural history of the primary disease process or expected complications of critical illness will not be reportable as serious adverse events.

The principal investigator at a site will need to distinguish between an SAE that is possibly, probably or definitely related to treatment (i.e. a suspected adverse reaction (SAR) – see definition below) and an SAE that arises from disease progression or has another cause.

The study intervention (dexamethasone) is a commonly used drug for which the safety profile is well established. For this reason, **only serious unexpected suspected adverse reactions (SUSARs) should be reported on an SAE form** for this trial.

The trial will also capture other serious adverse events (SAEs), which are pre-specified outcomes in the trial. These will not be reportable on an SAE form but will be captured on the CRF and include the following:

- Death due to progression of the underlying disease or co-morbid illness
- Admission to the intensive care unit due to progression of the underlying disease or co-morbid illness
- Prolongation of hospital stay due to progression of the underlying disease or co-morbid illness

8.1 Definitions

8.1.1 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal product, which does not necessarily have to have a causal relationship with the treatment (the study medication) that at any dose:

- Results in death,
- Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events (NOTE: Other events that may not result in death are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.)

8.1.2 Serious Adverse Reaction (SAR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the trial treatment qualify as adverse reactions.

8.1.3 Expected Serious Adverse Reactions (Expected SAR)

An adverse reaction, the nature or severity of which is consistent with the applicable product information.

8.1.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A serious adverse reaction, the nature or severity of which **is not** consistent with the summary of product characteristics. Dexamethasone is an established drug with a well-known safety profile and therefore the occurrence of SUSARs in this trial is unlikely.

8.2 Reporting procedure

Serious unexpected adverse reactions (SUSARs) are expected to be rare in this trial, however **all** SUSARs should be reported on an SAE form within 24 hours of being made aware of the event to the Sponsor.

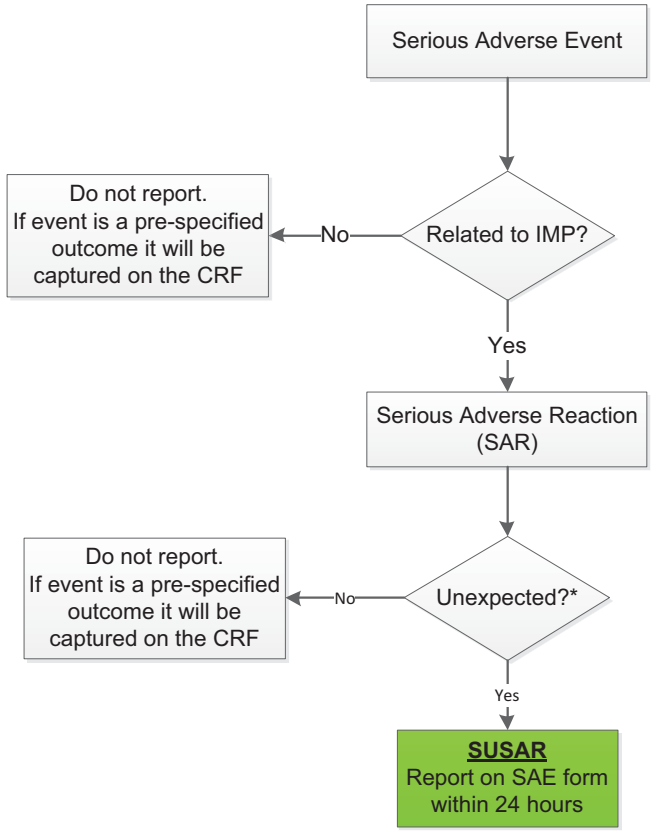
The fax number for reporting of SUSARs will be supplied to trial sites once the decision to activate the trial has been made.

All other serious adverse events and serious adverse reactions will not be reported. Where they are a pre-specified outcome for the trial they will be collected on the CRF.

The flow chart in

Figure **4** should be used to determine whether an SAE requires reporting on an SAE form.

Figure 4: Flowchart for reporting of serious adverse events



* the event is not consistent with the summary of product characteristics

9 STATISTICAL CONSIDERATIONS

A separate detailed statistical analysis plan will be written and approved by the Trial Steering Committee during the set up phase. The trial is planned in anticipation of a high severity pandemic; this represents the most challenging situation for trial execution and also the situation in which the trial results might have the largest public health impact. At the outset of a pandemic, its severity will not necessarily be accurately appreciated. The statistical plan therefore includes the flexibility to address pandemics of different severity. A review of pandemic severity will be conducted by the TSC as the pandemic unfolds. Decisions regarding the final analysis plan and final primary outcome will rest with the TSC. A summary of the plan is described below.

9.1 Description of Statistical Methods

We will compare numbers, age and sex of randomised participants with aggregate summary data of all patients admitted to hospital with influenza-like illness during the study period. We will compare baseline characteristics of the randomised arms using appropriate descriptive statistics. Between-group comparisons for primary and secondary outcomes will be conducted using an intention-to-treat (ITT) approach, implemented using appropriate regression models, and with results presented as point estimates such as a ratio or difference comparing dexamethasone with placebo, with 95% confidence intervals, and exact p-values. Secondary analyses will include additional adjustment for variables displaying an important imbalance at baseline. We anticipate little, if any, missing primary outcome data and therefore will use ITT without imputation as the main approach, and will investigate the influence of any missing data in sensitivity analyses, including multiple imputation. A definition of the pandemic as high, moderate or low severity is expected soon after the end of the first wave, and analysis of the appropriate primary outcome, and such secondary outcome data as are available, will then ensue in time to inform subsequent pandemic waves. All analyses will be conducted using Stata version 11.2 or higher, or MLwiN 2.10 or higher.

It is possible that a small number of participants will be randomised more than once. We will examine baseline (at first randomisation) characteristics and previous treatment allocation(s) of participants randomised more than once using appropriate descriptive statistics. The primary analysis will use treatment allocation and date of the first randomisation. In sensitivity analyses, we will (1) further adjust for variables associated with multiple randomisation (baseline characteristics and initial treatment allocation), and (2) use treatment allocation and date of the last randomisation.

High Severity Pandemic

In a **high severity pandemic,** the **primary composite outcome is admission to intensive care or death by Day 30, and** will be analysed using generalised linear modelling for binary outcomes, also allowing for stratification by site. Additionally, death will be reported alone as a secondary outcome.

Low/Moderate Severity Pandemic

In a **low/moderate severity pandemic,** the **primary outcome is time to hospital discharge, right-censored at 30 days, and** will be analysed using appropriate (dependent on distribution of the outcome) time-to-event regression modelling, also allowing for stratification by site and for the occurrence of death prior to hospital discharge as a competing event.

Pre-planned sub-group analyses will be conducted for the primary outcome based on the following baseline factors:

1) Duration of symptoms before trial entry: less than 4 days; more than 4 days; not known
2) Clinical diagnosis of pneumonia at trial entry: pneumonia; no pneumonia; not known
3) Underlying co-morbid illness at trial entry (defined as any medical illness requiring active regular treatment): underlying co-morbid disease, no underlying co-morbid disease; not known
4) Severity of influenza at trial entry (severe influenza defined as the presence of 3 or more community triage criteria [28]): severe influenza; not severe influenza; severity unclear/ not known.

Outcomes will be reported descriptively by sub-group category and treatment arm, and formally estimated by fitting interaction terms in the regression models. It is recognised that power to detect sub-group effects is likely to be low, and these analyses will be regarded as exploratory and interpreted with due caution.

9.2 The Number of Participants

The planned sample size of 2200 patients is based on a high severity pandemic along a range of possible scenarios. This flexibility is important as the accuracy of the modelling may only become clear as the pandemic unfolds.

Based on data from the Department of Health, modelling estimates are that, for a high severity pandemic, 35% of those admitted to hospital will die and 25% will be admitted to intensive care. Of those admitted to intensive care, an estimated 50% will die (estimate derived from UK data related to the 2009 pandemic and to community acquired pneumonia). Thus 47.5% will have the composite outcome of death or admission to hospital in the control group. For this scenario, our study would have 90% power to detect a 15% reduction in relative risk of the composite outcome associated with steroids, and a 20% reduction in deaths. Since a high proportion of those admitted to hospital will die and admissions to intensive care will also be high, therefore, an effect size of 15% would be clinically important.

Table 2 presents a range of scenarios centres around a control event rate of 47.5%.

Table 2: Sample size calculations for a high severity pandemic

Control event rate	Relative risk reduction with dexamethasone treatment	N* (80% power)	N* (90% power)
35%	20% 15%	1514 2704	2006 *3592*
40%	20% 15%	1242 2210	1644 2932
47.5%	20% 15%	940 1662	1242 2204
50%	20% 15%	860 1514	1134 2010

** Sample size estimates in each cell have been inflated by 5%, to allow for lack of compliance and loss to follow-up (both anticipated to be low)*

For low and moderate severity pandemics, a Hazard Ratio of 1.25, indicating an increased risk of discharge at any given time, is considered as the minimum clinically relevant change to detect. The sample size estimation method is the log rank test allowing for competing risks, and assumes that in the control group 5% are censored at 30 days, and in both groups, 6% (low severity pandemic) and 10% (moderate severity pandemic) die during hospitalisation. With 90% power and 1% two-side alpha, and allowing for 5% non-collection of primary outcome data, a total of 912 and 924 participants are required to be randomised for low and moderate severity pandemics respectively.

The target sample size for the study is 2200. If the pandemic is of low or moderate severity, it is likely that fewer than 2200 participants will be randomised during the first wave of approximately six weeks duration, although this definition will not be available until after the end of the first wave. If more than 924 participants are randomised in a low/moderate severity pandemic then smaller effect sizes may be detectable.

9.3 Interim Analyses

The objective of the trial is to complete recruitment within the first pandemic wave. Typically, a pandemic wave is of 6 weeks' duration. Therefore, it is expected that there will be insufficient time to perform a meaningful interim analysis based on efficacy data prior to close of recruitment. An early analysis will be

conducted at the close of recruitment and before the second pandemic wave. Given the timeframes involved, this early analysis will report on the primary outcome and as many other outcomes as possible.

9.4 Procedure for accounting for missing, unused, and spurious data.

The reason for missing data will be checked. Sensitivity analysis will be performed prior to imputation of missing data. If imputation is required, multiple imputation will be considered if data missing are at random. Otherwise, a selection bias collection model within a mixture model framework will be considered.

Both missing data and spurious data will be queried.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, NCTU, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

A Trial Steering Committee (TSC) has been established which includes an independent chair, two independent members and patient representatives. The TSC will meet to discuss and agree the final protocol version, and it will approve the Statistical Analysis Plan before the trial data are unblinded.

The TSC have agreed to meet (either in person or by telephone) every three years during the hibernation phase. A yearly report will be produced by the TMG and sent to the TSC. Should any of the information contained in the report warrant a meeting this will be arranged.

The TSC will be responsible for activating the trial in consultation with the TMG, NIHR and Department of Health.

An independent Data Monitoring Committee (DMC) will be established and will act in accordance with the pre-agreed terms of reference. Only the DMC will have access to unblinded data until the final assessment has been completed.

The Trial Management Group (TMG) will be responsible for day-to-day supervision of the study. Membership will include the CI, the trial manager and at least one other member of the NCTU. The TMG will be responsible for ensuring project milestones are achieved. The TMG will meet monthly during the set up phase, 6 monthly during the 'hibernation' phase, and every 2 to 8 weeks during the activation phase (depending on need). The TMG will report at least annually to the TSC.

Recruitment rates at sub-study sites will be monitored closely by the Trial Management Group TMG and TSC.

12 ETHICS

12.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

12.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

12.3 Approvals

Trial documents including the protocol, consent documentation, participant information sheet, postal questionnaire and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC). Required documents will also be submitted to the regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. Each participant will be assigned a Participant ID number, allocated at randomisation, for use on trial documents and the trial database. The documents and database will also use the patient's initials. The patient's date of birth will also be entered into the database.

The participants will be identified only by participant ID number on the trial database and on the follow-up questionnaire returned to the NCTU. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act.

12.5 Other Ethical Considerations

There are no additional ethical considerations.

13 DATA HANDLING AND RECORD KEEPING

All trial data will be entered onto a trial specific macro system, via a secure web browser session. Access to the system will be restricted and secure using password protection. All data will be stored on a secure server. Access will be restricted by user identifiers and passwords.

Electronic data will be backed up every 24 hours to a remote secure encrypted server.

For the follow up questionnaire and registration of participants with the HSCIC, identifiable information about participants will be held in a separate area of the system. Access to this information will be restricted to those involved in the follow up phase, as authorised by the Chief Investigator. Only the participant number will be used on the follow up questionnaire that will be posted back to NCTU.

14 FINANCING AND INSURANCE

This study is funded through the NIHR Programme NETSCC Pandemic Flu personal award (11/46/14). Nottingham University hospitals NHS Trust will act as the main sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in this trial. Standard NHS Indemnity applies.

15 PUBLICATION POLICY

The study has been designed and will be reported according to the CONSORT guidelines. The findings from this study will provide robust evidence for clinicians working in acute medical services including Emergency Departments. Findings will be published in peer-reviewed scientific journals, medical society newsletters and where possible in the local press and media. The results will be presented at national and

international conferences. Participants who requested a copy of the report will be sent a lay summary of the study

16 HEALTH ECONOMICS

A provider perspective for costs will be adopted. For patients in both the test and the control arms, management will entail up to 4 different episodes of hospital stays, plus primary care visits following discharge. The cost for each patient is therefore the sum of the following (where IP = inpatient, LOS = length of stay, in days).

- Cost of initial IP admission = cost of IP stay per diem * LOS1.
- Cost of readmission = cost of IP stay per diem * LOS2.
- Cost of intensive/critical care = cost of ICU per hour * LOS3 * 24
- Cost of intervention-related complications = cost of IP stay per diem * LOS4.
- Primary care costs = cost per GP consultation * number of condition-related consultations.

The trial will record the 4 types of IP LOS and GP visits for each patient, enabling calculation of patient specific health system costs (following multiplication by the appropriate units costs).

For patients admitted to critical care, separate national tariffs for critical care which have been developed in relation to the number of organs supported (zero to six, reference costs currency codes XC07Z to XC01Z) will be used to attribute critical care costs weighted by degree of support to each subject under treatment.

From a health outcome point of view, the only difference between the trial arms will be in their death rates. Given the age at death for each patient, the expected total and average life years lost in each arm using conventional life-tables will be calculated.

The results will be expressed as the:

- Average management cost per patient for each arm.
- Incremental cost-effectiveness ratio (mean cost per life year gained, test arm relative to control).

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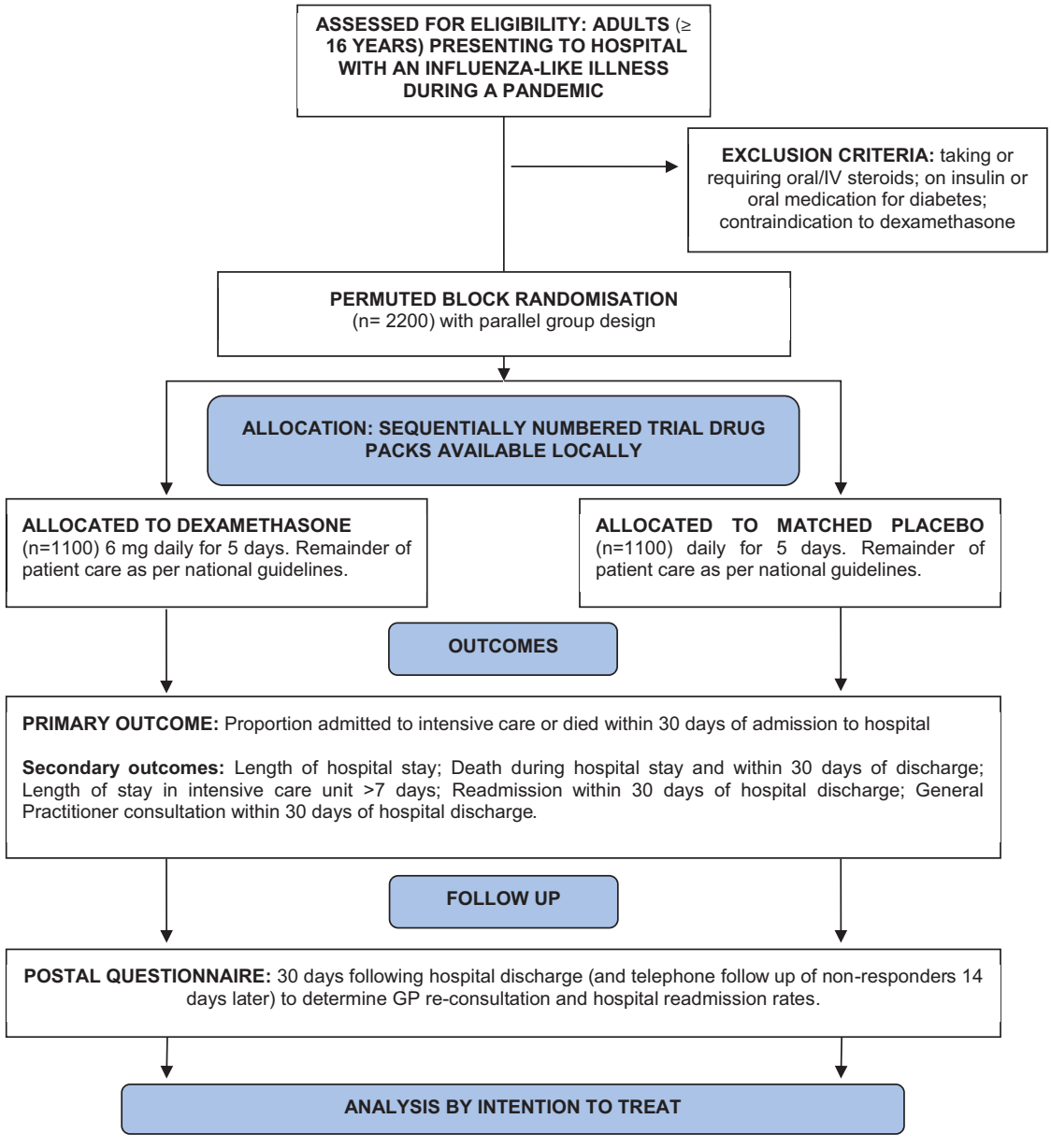
APPENDIX A – TRIAL FLOW CHART



AT THE OUTSET OF A PANDEMIC, ITS SEVERITY WILL NOT NECESSARILY BE ACCURATELY APPRECIATED. As the pandemic progresses a review of pandemic severity will be conducted by the TSC. Decisions regarding the final analysis plan will rest with the TSC

APPENDIX B – MECHANISTIC SUB-STUDY: DETERMINING THE INTERACTION OF STEROID THERAPY AND THE HOST

PLEASE NOTE THAT THIS SUB-STUDY WILL ONLY BE CONDUCTED AT THE FOLLOWING SITES:

1) **Aintree University Hospital, Liverpool**
2) **City Hospital, Nottingham**
3) **Manchester Royal Infirmary**
4) Queen's M edical Centre, Nottingha m
5) **Royal Liverpool University Hospital**
6) **Southampton General Hospital**

IMPORTANT: THIS APPENDIX IS ONLY APPLICABLE TO THE ABOVE LISTED SITES.

Aims

This mechanistic sub-study aims to address the following key questions in the treatment of influenza:

a) For each patient, what was the point in the natural history of influenza infection at which admission occurred?
b) What effect dose steroid have on the natural history of influenza infection defined by clinical phenotype and RNA transcriptomic pattern?
c) Does comparison of the transcriptomic pattern in placebo versus steroid treated arm suggest pro-inflammatory and anti-inflammatory mechanisms are both altered?

Background

The NIHR have recommended that a mechanistic sub-study be conducted as part of the ASAP trial. This sub-study will be conducted in a limited number of pre-selected ASAP trial sites. These sites have been selected as they are considered to have sufficient staff and infrastructural capacity to manage the additional work related to the sub-study without compromise to clinical care delivery or conduct of the main ASAP trial.

The onset of symptoms is highly variable in influenza exposed adults[1] and the severity of symptoms is the result of a complex host-pathogen interaction[2] altered by co-infection and co-morbid illness[3]. Initially, cytokine data were used to describe this interaction, but recent data from a unique human influenza challenge study have fully described the human inflammatory and anti-inflammatory pathways that determine symptom severity in exposed adults[4]. Using whole genome arrays (Affymetrix Human Genome U133A v2), 5076 genes showed altered expression during the 5 days following influenza A exposure. Unsupervised and clinically informed analyses resulted in self-organising maps (clustered gene expression patterns) which showed 8 functionally important gene sets in which activation/inhibition was tightly associated with clinical severity (see reference 4). The study also described the duration in hours between virus exposure and significant difference in self-organising map (SOM) cluster expression between symptomatic/asymptomatic subjects.

Thus, this sub-study will apply the best contemporary (with respect to the time of pandemic declaration) methods to a representative sample (n=200) of ASAP trial participants in order to determine the interaction of steroid therapy and the host and to apply this in interpreting the clinical outcome measured.

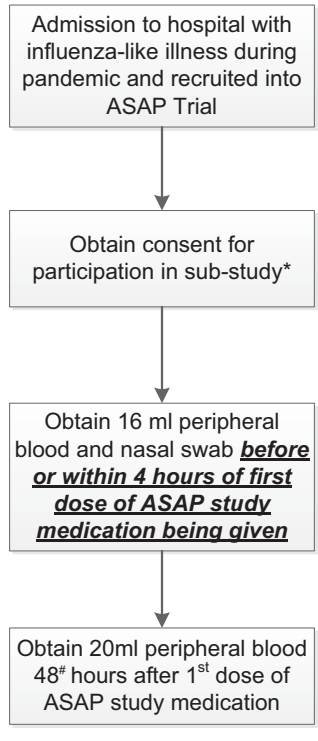
Methods/Design

Patients recruited into the ASAP trial at the sub-study sites will be given the opportunity to participate in the sub-study. 200 patients who have received ASAP study medication are required for the sub-study.

ASAP trial participants who consent to participation in the sub-study will give two blood samples and have one nasal swab taken for subsequent transcriptomic and microbiological testing. Blood samples will be collected into vaccutainer tubes at baseline and 48 hours post first dose of ASAP study medication. These time points are practical and match the best available transcriptomic data and the expected time course of steroid effect on gene expression. These samples can be collected using standard venesection methods and transferred without urgency to frozen storage in the hospital clinical laboratories. These sample collections should therefore be minimally obstructive in the context of a pandemic. The nasal swab for virological confirmation will be obtained at the time of the first blood sample collection. Please see figure 1 for an overview of the sub-study design.

The overarching principle in relation to the conduct of the mechanistic sub-study is that it should not disadvantage or jeopardise conduct of or recruitment into the main ASAP trial. Six sites have been selected to participate in the sub-study and the decision to activate the sub-study and these sites will be determined by the Trial Management Group according to pre-agreed criteria. The ability of these sites to conduct the sub-study will continue to be monitored by the Trial Management Group throughout the recruitment phase.

Figure 1: Overview of the sub-study design



* Blood and nasal samples are required at the latest 4 hours after first dose of study medication so consent must have been obtained prior to the samples being taken.

Sample should be obtained at 48 hours (+/- 3 hours) or at discharge if this is sooner

Participants and recruitment
All patients recruited into the ASAP trial at sub-study sites will be eligible to participate in the sub-study.

In order to fulfil the sampling requirements, recruitment into the sub-study **should only be considered where it is practically possible to obtain consent for the sub-study and take the first blood sample required for the sub-study either before the participant receives their first dose of ASAP study medication or within 4 hours of the first dose of ASAP study medication being administered.**

ASAP trial participants will be approached by a doctor or nurse following consent into the ASAP trial, either at the point of recruitment into the ASAP trial or shortly after being recruited into the ASAP trial.

Consent must be obtained for all patients recruited into the sub-study in a similar manner as for the ASAP trial to ensure a representative sample of participants.

A separate sub-study patient information sheet and consent form will be used.

The procedure for obtaining consent for the sub-study is as follows:

Patients with capacity to consent (non-emergency situation)

ASAP trial participants will be provided with a sub-study patient information sheet and a doctor or nurse will give a verbal explanation of the study. It will be clearly stated that the patient is free to withdraw from the sub-study at any time and for any reason without affecting their future care, and with no obligation to give the reason for withdrawal. The ASAP trial participant will be given the opportunity to ask any questions and if they agree to participate in the sub-study they will be asked to sign a consent form. The participant must personally sign and date the latest approved version of the informed consent form before any sub-study procedures are performed. The person obtaining consent must be suitably qualified and experienced, and have been authorised to do so by the ASAP Trial Principal Investigator.

Once written consent has been obtained, the patient will be enrolled onto the sub-study.

Patients with capacity to consent (emergency situation)

In the same manner described in the ASAP trial protocol, where a patient has capacity to consent but is in an emergency situation whereby it is not medically appropriate to delay the start of the ASAP study treatment, one **independent doctor** should consider the patient's eligibility criteria and any known views of the patient about participation and decide whether or not to enrol the patient into the sub-study.

Once the decision has been made to enter the patient into the sub-study this must be documented by the clinician in the patient's medical notes. The participant may then be enrolled into the sub-study. Written consent must be sought later.

Patients without capacity to consent

If, in accordance with the ASAP trial protocol a patient is judged to lack capacity to consent, one **independent doctor** should consider the patient's eligibility criteria and any known views of the patient about participation and decide whether or not to enrol the patient into the sub-study.

Once the decision has been made to enter the patient into the sub-study this must be documented by the clinician in the patient's medical notes. The participant may then be enrolled into the sub-study. Written consent must be sought later.

Written consent for patients that lacked capacity at enrolment and emergency situations

For patients who lack capacity to consent at enrolment or patients with capacity that are entered into the trial under emergency situation regulations, written consent must be obtained by a doctor or an appropriately trained nurse from the participant (if capacity has been recovered) or Personal Legal Representative as soon as it is practicable to do so.

A Personal Legal Representative may be a partner, friend or relative.

The participant's decision to withdraw from the sub-study would overrule any decision made by a doctor or Personal Legal Representative.

Sampling requirements

Sub-study participants will give two blood samples and a nasal swab for sub-study purposes. All samples will be obtained by an appropriately trained doctor or nurse.

Table 1 provides a summary of the samples required.

Table 1: Sub-study sample requirements

Time point	Sample	Details
Baseline (after recruitment into ASAP trial and before, or within 4 hours of 1st dose of ASAP study medication)	16 ml peripheral blood	2 x 2.5 PAXgene tubes (RNA expression analysis) 1 x 6ml plasma gel tube (corticosteroid pharmacokinetics) 1 x 5ml serum gel tube (multiplex cytokine array)
	Nasal swab	Collected in standard viral transport medium. This sample will be in addition to any nasal swab taken for clinical purposes, but may be taken at the same time-point if appropriate.
Mid-treatment (48 hours (+/- 3 hours) after 1st dose of study medication, or prior to hospital discharge, whichever is sooner)	20 ml peripheral blood	1 x 5ml plasma gel tube (corticosteroid pharmacokinetics) 1 x 5ml serum gel tube (multiplex cytokine array) 1 x 10ml EDTA tube (genotyping)

Sample collection, storage and transport

Blood samples

A 16ml peripheral blood sample must be obtained before or within 4 hours of the first dose of ASAP study medication being given to the participant. Blood will be collected into 3 different tube types as outlined in Table 1. Of note, the PAXgene tubes should be collected last and should be used along with an extension adapter. Use of the adapter reduces the risk of reflux of the PAXgene preservative liquid during the blood draw.

A second 20ml peripheral blood sample must be obtained mid-treatment (at 48 hours (+/- 3 hours) after the first dose of ASAP study medication, or prior to hospital discharge, whichever is sooner).

Blood samples will be labelled with a unique sample identifier which will encode the study, participant trial ID number and the sample type and time point. All blood samples will be sent to the clinical laboratories at the hospital where the participant has been recruited. PAXgene tubes must stand at room temperature (RT) for at least 3 hours and no longer than 72 hours. They are then transferred to a standard -21°C freezer then when frozen racked and transferred to a -80°C freezer. The initial RT phase enables the RNA stabilisation solution to penetrate cells. The -21°C freeze prevents the glass bottle cracking when taken down to -80°C. Serum gel and plasma gel tubes will be labelled with similar unique identifiers. They should be spun and separated into 500uL aliquots which should be labelled, racked and frozen at -80°C.

All blood samples should be retained at site until recruitment to the sub-study has been completed. Frozen blood samples should then be sent by courier, on dry ice in a single batch to the Liverpool School of Tropical Medicine (LSTM) where they will be stored at -80°C until analysed. A Material Transfer Agreement (MTA) will be established between recruiting sites and LSTM to facilitate this.

Nasal swabs

A nasal swab must be taken on enrolment. Standard virus swabs with associated virological media will be used and provided in study packs to participating sites by the coordinating centre in Liverpool. All swabs will be promptly labelled and frozen to -80°C. All swabs will subsequently be transferred on dry ice to the Department of Virology, Royal Liverpool University Hospital where then will stored until analysis is performed.

Equipment for sampling

All materials related to the mechanistic sub study samples will be purchased by, and packs created in, Liverpool. These study packs will then be sent out to the sub-study sites.

Sample analysis

Blood samples

Once blood samples are received at the Liverpool School of Tropical Medicine, HTA compliant storage and archiving (Procuro system used for laboratory information) of blood samples will be provided in the Liverpool School of Tropical Medicine Respiratory Infection group.

Analysis of samples will be performed in a single batch using either RNA microarray expression analysis or next generation sequencing, depending on which is the most cost-effective method to obtain the data needed at the time analysis is carried out. This is a fast-moving technology and while the current balance would still favour microarray, it is anticipated that this will no longer be the case in a few years.

An inflammatory array of genes expressed during acute influenza (+/- steroids) will be described (using microarray or sequencing technology). These data will inform the clinical severity score, the duration of illness and most importantly will confirm the immune-modulatory effect of steroids

Nasal swabs

The latest test available to detect influenza virus including the pandemic strain will be used; this is expected to be a PCR test, however the specific test cannot be determined until the point of trial activation. After testing, all nasal swabs will be disposed of.

Surplus samples

Consent will be sought from sub-study participants for any remaining samples to be stored and used for future ethically approved research. Where consent has been given remaining samples will be stored in under a storage license from the Human Tissue Authority (HTA). Request for access to these samples for future ethically approved research will be made through the Chief Investigator and lead sub-study Investigator. Any outputs arising from use of these samples must reflect the contributions of both study teams.

Data collection

No additional data over and above that collection for the ASAP trial is required for the sub-study.

Withdrawal

Each sub-study participant has the right to withdraw from the sub-study at any time. In addition, the investigator may withdraw a participant from the sub-study at any time if the investigator considers it necessary for any reason. Any samples already collected for the sub-study would still be used unless specifically requested not to, in which case any samples collected would be destroyed.

The reason for withdrawal from the sub-study will be requested and recorded in the trial database, however participants are not obliged to give reasons.

There will be no replacement of participants who withdraw from the sub-study.

Statistical analyses

Data arising from the sub-study will be analysed by sub-study investigators at the Liverpool School of Tropical Medicine and University Hospital Aintree.

The following assumes that the platform chosen to achieve the stated aims is microarray analysis of the whole blood RNA transcriptome between subjects (placebo vs control) normalised to the transciptome of a set of healthy volunteers.

All analyses will be conducted in the latest version of R (currently 3.1.0). For analysis of the RNA transcriptome data we will use the latest version of the package Bioconductor (currently version 2.14). An initial normalisation step will be carried out to account for technical variation in the gene expression data between samples. Differential gene expression analysis will be explored between treatment and control samples using the normalised expression data.

- To address aim one, using day zero data, levels of expression of genes that defined temporal stage in the paper by Huang et al. will be summarised using appropriate descriptive statistics in order to define when in the course of flu infection patients were recruited to the study.

- To address aim two comparing steroid with placebo groups, between-group differences in the expression of relevant genes on day 3 will be estimated using appropriate regression models 4.

- To address aim three - functional analysis of genes of interest (those that are differentially expressed between treatment and placebo groups) will be performed to infer the mechanism of action of steroid when given to patients with pandemic influenza; this will be a descriptive analysis.

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