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Double-blinded randomised controlled trial of early low dose steroids in patients admitted to hospital with influenza infection during a pandemic

Adjuvant Steroids in Adults with Pandemic influenza

CLINICAL TRIAL PROTOCOL

Internal Reference No: 11RM013
Ethics Ref: Insert
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	NUMBER	DATE
DRAFT VERSION	1.1	12 December 2012
FINAL VERSION		
AMENDMENT (if any)		

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Sponsor:	Nottingham University Hospitals NHS Trust
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Signatures:	**Name & Role**	**Date**	**Signature**
	Dr Wei Shen Lim Chief Investigator		
	Dr Maria Koufali Sponsor		

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust (s), regulatory authorities, and members of the Research Ethics Committee.

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1 AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2 SYNOPSIS

Study Title	Double-blinded randomised controlled trial of early low dose steroids in patients admitted to hospital with influenza infection during a pandemic.
Internal ref. no.	11RM013
Clinical Phase	Phase 3
Trial Design	Pragmatic multi-centre double-blind randomized trial
Trial Participants	Adults (> 16 years old) hospitalised with an influenza-like illness during a pandemic.
Planned Sample Size	Our planned sample size of 2,200 patients is based on the range of possible scenarios that might be encountered during a pandemic. With 2,200 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	Thirty days after hospital discharge
Planned Trial Period	The trial is unique as it will be set up pre-pandemic then placed in hibernation with all necessary approvals in place. The trial will only be activated in the event of a pandemic. The planned activation phase is 4 months, including a 4-week pre-activation phase when certain trial elements will be activated prior to recruitment. It is planned to complete recruitment within the first pandemic wave, typically of 6 weeks duration.
Primary Objective	To determine whether during a pandemic, in adults hospitalised with an influenza-like illness, a 5-day course of dexamethasone started within 24 hours of admission, 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 is associated with reductions in length of hospital stay, hospital readmission and/or post-discharge GP consultation compared to placebo. The cost-effectiveness of the intervention will also be determined.
Primary Endpoint	Admission to intensive care unit or death, within 30 days of admission
Secondary Endpoints	1. Length of stay in intensive care unit > 7 days 2. Readmission within 30 days of hospital discharge 3. Consulted GP within 30 days of hospital discharge 4. Length of stay in hospital 5. Death in hospital The statistical plan includes the flexibility to adjust for pandemics of different severity.
Investigational Medicinal Products	Dexmethasone, given as adjuvant therapy in addition to standard care.
Form	Liquid
Dose	6 mg once daily for 5 days from the day of hospital admission
Route	Oral

3 ABBREVIATIONS

AE	Adverse event
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference of Harmonisation
ICU	Intensive Care Unit
LOS	length of stay in hospital
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions

4 BACKGROUND

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; CRF 0.1 to 0.4%. In contrast, the 2009 pandemic (H1N1) was much less severe affecting mainly people aged below 55 years of age, and with a case-fatality ratio (0.025%) in the UK similar to that of recent seasonal influenza viruses (Donaldson, Rutter et al. 2009). 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 needs 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. Most persons might be expected to experience a minor influenza-like illness characterized by fever and cough typically lasting 7 to 10 days. For pandemic planning purposes, the UK Pandemic Influenza Preparedness Strategy 2011 recommends that between 1% and 4% of symptomatic patients should be expected to require hospital care.(Team 2011) Patients may be admitted to hospital because of influenza-related exacerbations of underlying co-existing illnesses such as chronic obstructive pulmonary disease (COPD) or 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;(Nguyen-Van-Tam, Openshaw et al. 2010) 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 (Nguyen-Van-Tam, Openshaw et al. 2010) .

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 (2006). 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 (Lee, Wong et al. 2007).

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 (de Jong, Simmons et al. 2006). Similar changes have been observed in patients with 2009 pandemic H1N1 infection (Bermejo-Martin, Ortiz de Lejarazu et al. 2009). 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 (Prigent, Maxime et al. 2004). 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 (Rhen and Cidlowski 2005; Kaufmann, Briegel et al. 2008).

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 (Kumar, Zarychanski et al. 2009; Annane ; Matthay and Liu 2011; Quispe-Laime, Bracco et al. 2011). 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 (Brun-Buisson, Richard et al. 2011), 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 (Martin-Loeches, Lisboa et al. 2011). The heterogeneity of these cohort studies and non-randomized study designs preclude any firm conclusions regarding the risks or benefits of corticosteroids in influenza.

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) (Meijvis, Hardeman et al. 2011). 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) (Snijders, Daniels et al. 2010). 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 (Mikami, Suzuki et al. 2007).

In patients with severe community acquired pneumonia admitted to intensive care (ICU) (Confalonieri, Urbino et al. 2005), 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 (Annane, Bellissant et al. 2009) 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

In 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 (Brun-Buisson, Richard et al. 2011; Kim, Hong et al. 2011; Martin-Loeches, Lisboa et al. 2011; Quispe-Laime, Bracco et al. 2011). Some cohort studies observed an association of corticosteroids with an increase in **hospital acquired pneumonia**, including fungal pneumonia (Brun-Buisson, Richard et al. 2011; Kim, Hong et al. 2011; Martin-Loeches, Lisboa et al. 2011; Quispe-Laime, Bracco et al. 2011). 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) (Han, Ma et al. 2011).

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) (Snijders, Daniels et al. 2010; Meijvis, Hardeman et al. 2011). 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 (prednisoloine v 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) (Brouwer, McIntyre et al.). 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.

Description of study intervention

The study intervention comprises dexamethasone administered as an oral liquid preparation, within 24 hours of hospital admission, at 6 mg daily for 5 days. 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 offer protection against late failures due to rebound inflammation.

The oral liquid preparation will enable the vast majority of eligible patients to receive the intervention except those who are either strictly ‘nil by mouth’ or are unable to swallow. For some of these patients, 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 of patients on intensive care received ‘off-licence’ intravenous antiviral therapy.

Dexamethasone 6 mg is equivalent to prednisolone 40 mg or hydrocortisone 160 mg.

5 OBJECTIVES

5.1 Primary Objective

To determine whether during a pandemic, in adults hospitalised with an influenza-like illness, a 5-day course of dexamethasone started within 24 hours of admission, 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

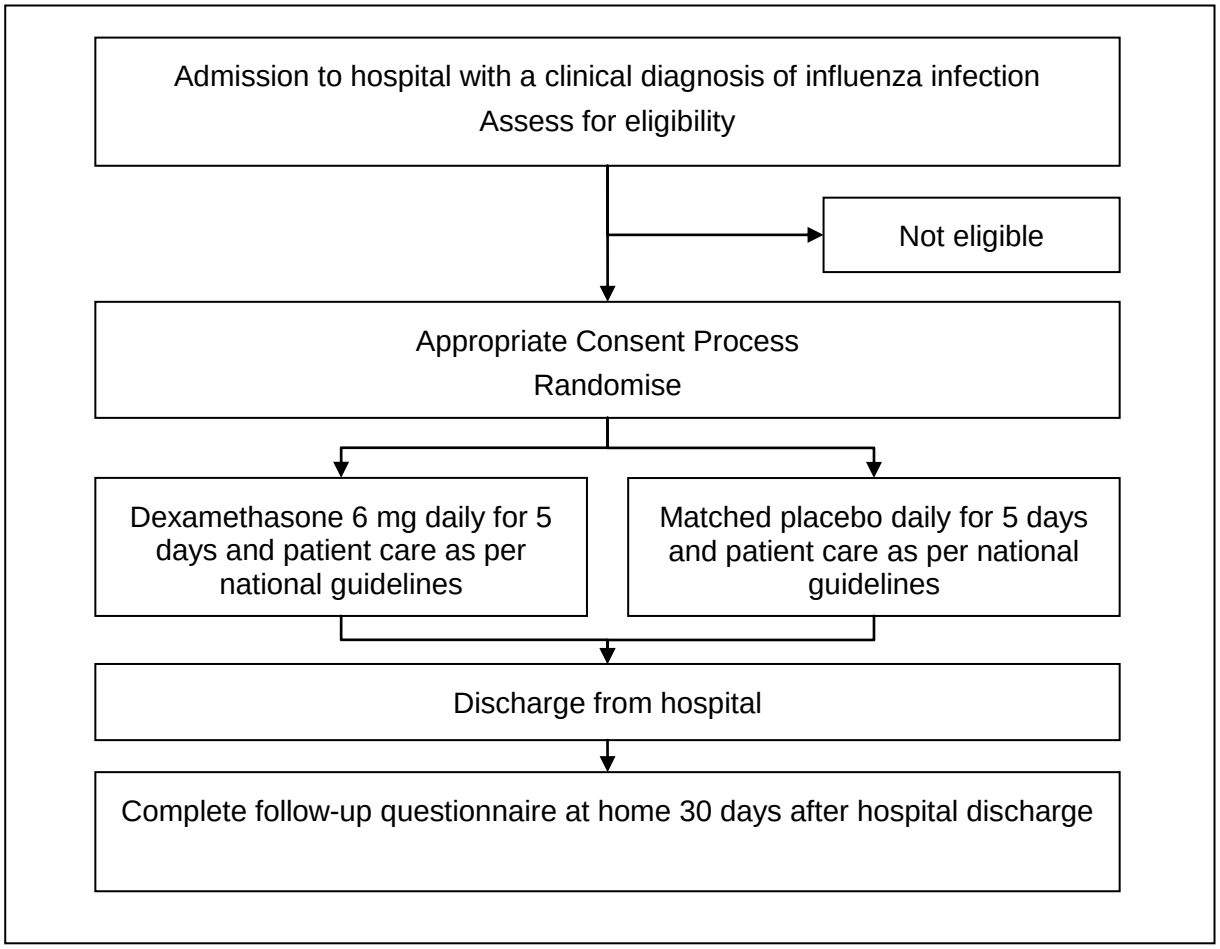
To determine whether dexamethasone given in addition to standard care is associated with reductions in length of hospital stay, hospital readmission and/or post-discharge GP consultation compared to placebo. The study will also evaluate the cost-effectiveness of the intervention.

6 TRIAL DESIGN

6.1 Summary of Trial Design

This 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.

Patient flowchart



Participants are in the trial from randomisation until they have returned the follow-up questionnaire. The trial treatment is given over 5 days while they are in hospital, or continued at home if discharged within 5 days of admission. All other care is according to national clinical

management guidelines for pandemic influenza. Participants do not have any study visits and are only required to complete a follow-up questionnaire 30 days after hospital discharge.

6.2 Outcome Measures

6.2.1 Primary outcome

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

6.2.2 Secondary outcomes

1. Length of stay in intensive care unit > 7 days
2. Readmission within 30 days of hospital discharge
3. Consulted GP within 30 days of hospital discharge
4. Length of stay in hospital
5. Death in hospital

6.3 Trial Participants

6.3.1 Overall Description of Trial Participants

Adults admitted to hospital with a clinical diagnosis of influenza infection during a pandemic.

6.3.2 Inclusion Criteria

During a pandemic, patients are eligible for recruitment if they:

- Are over > 16 years of age
- Are admitted to hospital within the last 24 hours with a clinical diagnosis of an influenza-like illness, and
- The appropriate consent procedures have been carried out.

The diagnosis of an influenza-like illness will be based on the WHO definition: sudden onset of fever (≥38ºC), and cough or sore throat, and the absence of other diagnoses to explain these symptoms.

6.3.3 Exclusion Criteria

Patients are not eligible for recruitment if they:

- Are taking corticosteroids at the time of hospital admission, or require corticosteroids for other clinical reasons
- Are on oral medication or insulin for the management of diabetes mellitus
- Have a contra-indication to dexamethasone

6.4 Study Procedures

Patients recruited into the trial will receive dexamethasone 6 mg or placebo as a liquid solution once daily for 5 days, administered orally. Data on primary and secondary outcome measures will be collected by site investigators from routinely available data at hospital discharge or Day 30 (whichever comes sooner). Follow-up data will be collected by Nottingham CTU at 30 days after discharge by postal questionnaire (or telephone interview of non-responders 14 days later.

Study procedures

Assessments	Day 1 Screening and enrolment	Day 2	Day 3	Day 4	Day 5	Hospital discharge/ Day 30*	Follow-up 30 days after hospital discharge
Screen for eligibility	X						
Consent Process	X						
Complete baseline information	X						
Randomise	X						
Administer trial treatment	X	X	X	X	X		
Collect primary and secondary outcomes from Hospital notes*						X	
Collect follow-up outcomes from postal questionnaire							X

* The data is collected at hospital discharge when the discharge is less than 30 days since admission. The data is collected at day 30 if the participant remains in hospital.

6.4.1 Study Consent

The challenges of obtaining consent for a trial in an emergency setting are recognised. It is also acknowledged that delays consequent on the consent process should be reduced to the minimum. (Roberts, Prieto-Merino et al. 2011) Additional pandemic-specific factors further inform the approach to consent in this study.

A) Patients admitted to hospital with severe pandemic influenza constitute a medical emergency. Such patients can deteriorate rapidly (within hours admission to hospital) and dramatically; the average time from hospital admission to ICU admission was 1 day in the 2009 pandemic.

B) 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. How these factors will affect local service delivery will depend on the clinical severity of the pandemic strain, geographical spread of the pandemic (distribution of 'hot spots') and resilience of local systems. These challenges to the clinical service during a pandemic impact significantly on research delivery as well.

C) The UK Pandemic Plan (2011) describes a proportionate response to pandemics of different impact. In moderate and high impact circumstances, it is recognised that hospital services may not be able to continue all usual activity; this may of necessity be accompanied by alterations in clinical priorities. Such actions are grounded on firm ethical principles described in the Department of Health's document 'Responding to pandemic influenza: The ethical framework for policy and planning' (Gateway reference: 8891) - "*Planning for a pandemic, and responding to one while it is happening, involves many difficult decisions. These may create tension between the needs of individuals and the needs of the population". "Equal concern and respect is the fundamental principle that underpins this ethical framework."*

D) Even in a low impact pandemic, the UK Pandemic Plan acknowledges that maximal effort by hospital services may be necessary to cope with the increased pressures of a pandemic situation. Rapid patient flow away from hospital entry points will be necessary to enable

acute hospital services to receive and manage demand. Recruitment to research activity should not impede the acute clinical service.

The following approach has been developed with service users and patient representatives taking into account pandemic-related factors and the guidance in the UK Pandemic Plan 2011.

Overview of Consent Process proportionate to pandemic

Impact*	Healthcare Delivery*	Consent Process
Low – similar numbers of cases to seasonal influenza outbreaks AND vast majority of cases mild to moderate clinical features	Hospital services coping with increased pressures with maximal effort.	*Verbal assent on admission with deferred written consent obtained within 72 hours, and 'opt-out' provision*
Moderate/High – Higher number of cases than seasonal influenza AND/OR more severe cases	Health services no longer able to continue all activity	*Informed verbal assent on admission and 'opt-out' provision*
*descriptions from UK Pandemic Plan 2011.		

Prior information giving

Upon study activation, participating CLRNs will inform associated General Practices of the study and will encourage Practices to display brief information related to the study in Practice premises. Where appropriate, efforts will be made to increase community awareness of the study through local media channels; it is expected that media and public interest in pandemic news will be high.

During a pandemic, it is expected that patients presenting to hospital with an influenza-like illness (ILI) will be identified early and cohorting of patients will occur. Brief information about the trial will be made available to all patients with ILI at 'first contact' entry points to the hospital.

Patient has capacity to consent

If the attending clinician considers it appropriate, the potential participant will be asked if they are willing to be recruited to the study. Specifically, the responsible doctor will explain to the patient that they will receive the usual care for influenza infection but that in addition to this, the patient can be enrolled in a research study that aims to improve the treatment of patients with this condition. It will be explained that the study is being done to see whether using a drug called dexamethasone will help patients with influenza infection by reducing the risk of severe outcomes such as death or admission to intensive care or by reducing the length of stay in hospital. The patient will be informed that, if enrolled, they will be given a liquid solution once a day for 5 days of either dexamethasone or placebo (a dummy liquid that does not contain dexamethasone) orally or via an enteral feeding tube. The doctor will explain that in some studies, steroids such as dexamethasone, have been shown to improve outcomes in patients with other types of severe infections such as pneumonia, and that whilst we hope that it will also improve recovery after influenza infection, at present we cannot be sure about this.

The doctor will explain that should the patient agree to participate in the study, they will remain free to withdraw (opt-out) from the study at any subsequent time point. Further detailed written information about the study will be given at this time including the participant information sheet and contact details regarding the opt-out provision. If the patient agrees, verbal assent for participation in the study will be obtained and this will be recorded in the medical notes. Randomisation will follow.

In a low impact situation, written informed consent will be sought within 72 hours of admission. In the majority of cases, it is anticipated that written consent will be obtained within 24 hours and therefore prior to the second dose of dexamethasone/placebo on Day 2. If not already provided, the participant information sheet will be provided to the participant at this time. Participants will be given as long as they need to consider whether to give written consent, however we recommend that a maximum of 30 minutes should be taken obtaining written consent. The Consent Form will be signed and dated by the participant. If the participant is unable to write, witnessed verbal consent may be recorded on the consent form.

In a moderate or high impact situation, it will not be practically feasible to obtain written consent from all participants following initial verbal assent. This situation is also when the public health importance of this study may be largest and delay in study completion would potentially mean that study results would not be available to influence management within the same pandemic. As a proportionate response to this, verbal assent with opt-out provisions will be accepted as sufficient for participation in the study. The local investigator will inform the Chief Investigator within 3 days of a moderate or high impact situation being recognised locally. The Chief Investigator will be monitored by the Trial Steering Committee.

Patient lacks capacity to give consent

Lack of capacity will be determined by the participant's attending clinician. If the potential participant lacks capacity to give meaningful consent (e.g. in cases of confusion or reduced conscious level) the following procedure will be employed.

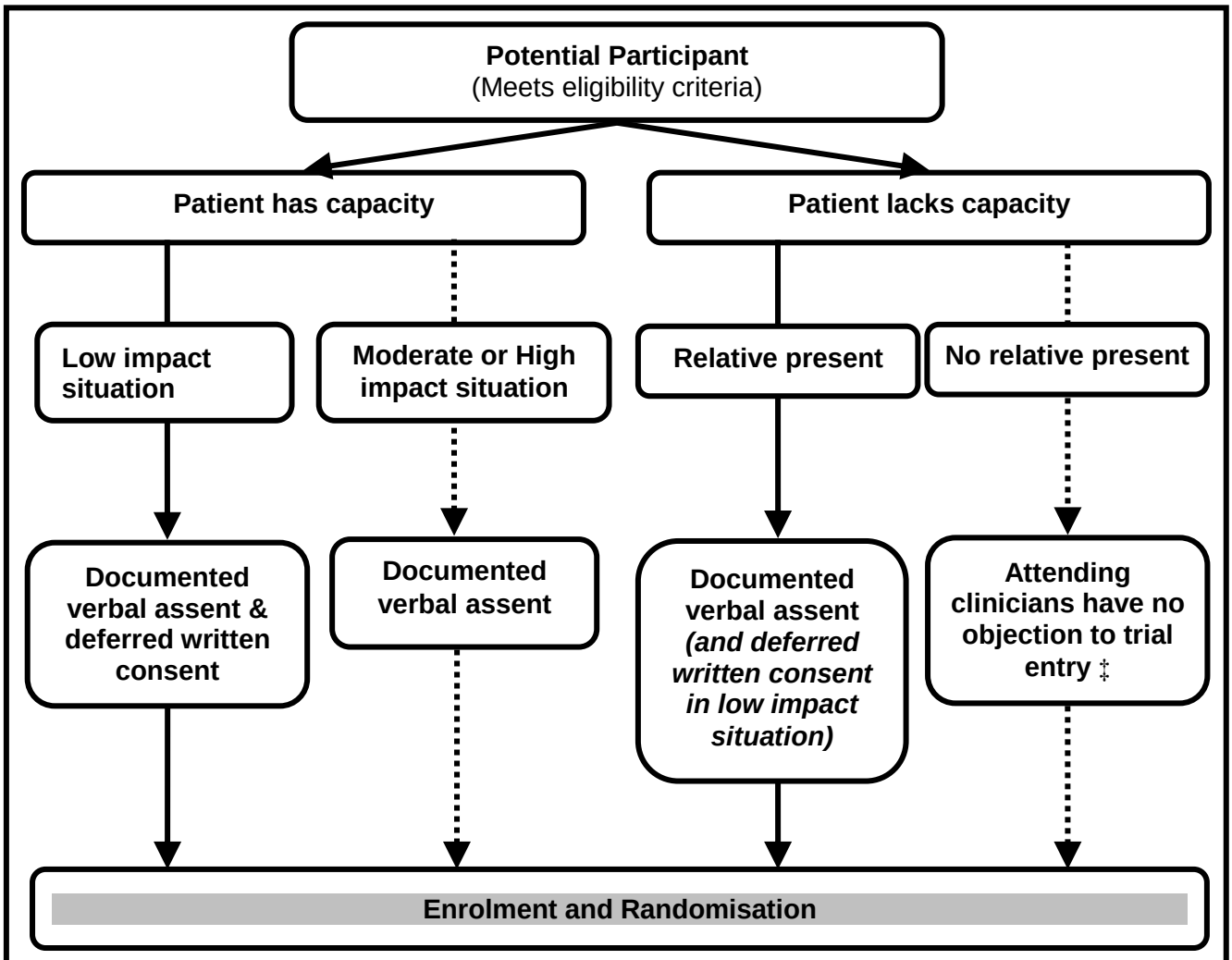
Relative present. If a relative (or other legal representative such as partner or close friend, able to represents the patient's views and wishes) is present, bearing in mind the clinical situation and their level of distress, they will be provided with brief information about the trial. Specifically, the responsible doctor will explain to the relative that the patient will receive the usual care for influenza infection but that in addition to this, the patient can be enrolled in a research study that aims to improve the treatment of patients with this condition. It will be explained that the study is being done to see whether using a drug called dexamethasone will help patients with influenza infection by reducing the risk of severe outcomes such as death or admission to intensive care, or by reducing the length of stay in hospital . The relative will be informed that, if enrolled, the patient will be given a liquid solution once a day for 5 days of either dexamethasone or placebo (a dummy liquid that does not contain dexamethasone) orally or via an enteral feeding tube.

The doctor will explain that in some studies, steroids such as dexamethasone, have been shown to improve outcomes in patients with other types of severe infection such as pneumonia and that whilst we hope that it will also improve recovery after influenza infection, at present we cannot be sure about this. Further detailed written information about the study will be given at this time including the participant information sheet and contact details regarding the opt-out provision. If the relative agrees, verbal assent for participation in the study will be obtained and this will be recorded in the medical notes. Randomisation will follow.

In a low impact situation, written consent will be sought from the relative within 72 hours of admission. In the majority of cases, it is anticipated that written consent will be obtained within 24 hours and therefore prior to the second dose of dexamethasone/placebo on Day 2.

If the relative objects to the inclusion of the patient in the trial, their view will be respected.

Consent Process flow chart



Patients or relatives will not be approached if there is insufficient time to give a brief oral summary of the trial, or they do not speak fluent English and no translator is available. If the patient (or relative if the participant lacks capacity) does not give verbal assent they will not be recruited.

‡ Patients with no relative present and lacking capacity to consent (e.g. unconscious) will be entered into the trial only if all of the attending clinicians (doctors and nurses) consider it appropriate. Patients will not be entered into the trial, if any of the clinicians present has an objection; in this case the patient will not be recruited. If clinicians have no objection to recruitment:

- A relative or the participant will be approached as soon as possible after recruitment to give written consent to participation in follow up and access to their data
- The Chief Investigator will be notified in 15 days and monitored by the Trial Steering Committee

Relative not present. If no relative is present, we intend to recruit a doctor, wherever possible unconnected with the trial, provide them with verbal information relating to the trial and obtain their verbal consent for the patient's inclusion in the trial. If a doctor unconnected with the trial is not available, as this is an emergency situation and it is not possible to delay the decision, the potential participant's treating clinician will review eligibility. If the treating clinician believes enrollment is in the patient's best interest, and attending clinicians (doctors and nurses) have no objection the participant will be enrolled. This is in accordance with Statutory Instrument 2006,

2984. Verbal assent will be obtained from the patient or their legal representative afterwards as soon as practicable, and this will be documented in the medical notes.

A participant who originally lacked capacity (and was entered into the study following agreement from a relative or legal representative) but then regained capacity will need to give documented verbal assent (or, in a low impact situation, written consent) to continue in the study. The participant's decision to withdraw would overrule the decision of the legal representative.

A participant may discontinue treatment either at their own request or if it is felt in their best interest by the attending physician. A participant who discontinues treatment (for whatever reason) will not be withdrawn from the trial unless the participant specifically withdraws (opts-out) for further follow-up. A participant may be withdrawn from the trial either at their own request (if they regain capacity) or at the request of the legal representative. The participant and the legal representative will be made aware that this will not affect the participant's future care. A participant who withdraws from the trial will be informed that data already collected prior to withdrawal cannot be deleted.

The requirements of the relevant ethics committee will be adhered to at all times. Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant.

6.4.2 Screening and Eligibility Assessment

During a pandemic, adults admitted to hospital with a clinical diagnosis of influenza infection 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.

The attending doctor will follow the appropriate consent process. If verbal assent is given, the trial pack label will be completed and the trial treatment prescribed. Participants will be considered to be in the trial once the pack label has been completed regardless of whether they receive the allocated treatment. Treatment in the pack will be administered as soon as possible, as an addition to standard care.

6.4.3 Baseline Assessments

There are no baseline assessments in this trial.

6.4.4 Randomisation and Code breaking

Allocation to trial treatment will be by taking the next in a consecutively numbered series of sealed trial packs. Nottingham CTU will generate and hold the randomisation sequence generation according to their SOP. Randomisation will be stratified by centre. Each pack will contain 75ml bottles of either dexamethasone 2mg/5ml (sufficient for 5 days of treatment) or placebo, plus stickers for the patient notes and drug chart. Packs will be available in each area where patients with influenza are likely to be admitted during a pandemic.

To minimise the potential for bias there will be a log of all packs, which will be checked daily and sent to NCTU. Packs which have been tampered with will be removed from the trial, and any packs used out of sequence will be investigated.

The study drug will be labelled with the study number and unique identification number. The two treatments dexamethasone and placebo will be indistinguishable.

Maintenance of randomisation codes and procedures for breaking code

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

In general there should be no need to unblind the allocated treatment. If some contra-indication to dexamethasone develops after randomisation (e.g. evidence of severe drug reaction), the trial treatment should simply be stopped. Unblinding should be done only in those rare cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received dexamethasone or placebo. In those few cases when urgent unblinding is considered necessary, the emergency telephone number should be used, giving the name of the doctor authorising unblinding and the trial pack number. The caller will then be told whether the patient received dexamethasone or placebo The rate of unblinding will be monitored and audited.

In the event of breaking of the treatment code this will normally be recorded as part of managing an SAE and such actions will be reported in a timely manner (notification of R&D within one working day of discovery or notification of the event).

6.4.5 Subsequent assessments

Hospital discharge or Day 30.

On hospital discharge or Day 30, if the participant remains in hospital, outcome data will be collected from the medical notes by site investigators and recorded on the CRF. The following outcome variables will be captured:

- Admission to intensive care
- Length of stay in intensive care
- Length of stay in hospital
- Death in hospital.

Follow-up

Follow-up data will be collected 30 days after hospital discharge. A questionnaire will be posted from the Nottingham CTU to participants asking about any re-admissions to hospital and/or consultations with their GP within 30 days of discharge. Participants who have not returned their completed questionnaire after 14 days will be contacted by telephone for this information.Telephone interview will be structured.

6.5 Definition of End of Trial

The end of trial is 60 days from the date of randomisation of the last participant.

6.6 Discontinuation/ Withdrawal of Participants

6.6.1 From the Study

Each participant has the right to withdraw from the study at any time. The reasons for leaving the study will be recorded, but participants are not obliged to give reasons. Participants will be assured that withdrawal will not affect the care they receive. They will be informed at the start of the study that data collected up to the point of withdrawal will be retained and may be used in the final analysis. There will be no replacement of participants who withdraw.

6.6.2 From the Study Treatment

Each participant has the right to withdraw from the study treatment at any time. If this happens, they will receive standard care. Participants will be analysed in their allocated group as "intention to treat" regardless of whether they received the intervention.

If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

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 (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

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 study the questionnaire will be used as the source document for 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, the participant will be referred to by the study participant number, not by name.

7 TREATMENT OF TRIAL PARTICIPANTS

7.1 Description of Study Treatment

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

Control Matched placebo solution once daily for 5 days, administered orally or via enteral feeding tube.

Dexsol (Dexamethasone) 2mg/5ml Oral Solution manufactured by Rosemont Pharmaceuticals Ltd (PLXXXX) will be used in this trial. Rosemont will also manufacture a matching placebo formulation at the point of trial activation. Rosemont bulk supply will be shipped to one or more of the following NHS manufacturing units: St Marys Pharmaceutical Unit (MIAIMPXXXX) Newcastle Specials Pharmacy Production Unit (MIAIMPXXXX) and Calderdale and Huddersfield Pharmacy Manufacturing Unit (MIAIMPXXXX). All three units will be set up to be able to provide the randomised final labelling, packaging and release service in order to ensure that 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 label a single 75ml bottle according to annex 13 and pack with measuring devices and written instructions in a clear outer pack so that the primary packaging label can be read through the pack. This includes an excess of treatment which will be destroyed at the end of the trial.

An outer dispenser pack of 10 participant packs will be assembled, in number order, from the finished active and placebo packs so that the packs can be removed in order.

The final product will be QP released by the designated person at the Manufacturing Unit.

The manufacturing unit where the packaging and release occurs will act as the central distributing pharmacy.

7.2 Storage of Study Treatment

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 pharmacy will supply stock packs of 10 individual participant packs to the areas within their hospital where influenza admissions occur. Pharmacy will operate a local top-up system to ensure that stocks are available at admission points.

Pharmacy will maintain a stock of participant packs to provide 'follow on' treatment to individual participants following a request from a trial physician. Follow on packs will be identified by the use of a web-based system designed and maintained by the NCTU. Each participating centre pharmacy will be provided with a Pharmacy File and take receipt of numbered supplies from the central pharmacy.

7.3 Compliance with Study Treatment

Compliance with trial treatment is expected to be good. Patients who are randomised but are then found not to have influenza based on clinically directed laboratory testing, may be advised by the attending clinician to stop the trial treatment. If it is not possible to administer the trial solution, the attending clinician will decide on clinical grounds whether or not to prescribe corticosteroids. If the patient is discharged before 5 days, they will be instructed to complete their trial treatment at home.

Compliance for hospitalised patients will be assessed from their medication chart which nursing staff will complete. Patients completing treatment at home will be asked in the follow-up postal questionnaire regarding compliance with trial medication following hospital discharge.

7.4 Accountability of the Study Treatment

The participant packs of study medication will be supplied by the central distribution pharmacy (St Mary's Pharmaceutical Unit, Newcastle Specials Pharmacy Production Unit or Calderdale and Huddersfield Pharmacy Manufacturing Unit) to the hospital pharmacy. All movements of study medication between the central pharmacy and pharmacy will be documented. Unused participant packs will be retrieved and accountability forms completed, before local destruction.

Pharmacy will record the distribution of all study medication to the admissions sites.

For participant who complete their treatment in hospital nursing staff will be asked to return part used treatment bottles to pharmacy. Participants who complete their treatment at home will be asked to dispose of any excess in the bottle as they would any other medication; by return to a local chemist. .

7.5 Concomitant Medication

Throughout the study Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the exclusion criteria. If these are required, the participant will be withdrawn. Any medication, other than the study medication taken during the study will be recorded in the CRF.

8 SAFETY REPORTING

(Refer to SOP 11 Adverse Events Monitoring, Reporting and Recording)

8.1 Definitions

8.1.1 Adverse Event (AE)

An AE or adverse experience is any untoward medical occurrence affecting a trial participantduring the course of a clinical trial. It does not necessarily have to have a causal relationship with the study medication. An AE can therefore be any unfavourable and unintended

sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

8.1.2 Adverse Drug Reaction (ADR)

All untoward and unintended responses to a medicinal product related to any dose.The phrase "responses to a medicinal products" 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 study medication qualify as adverse reactions.

8.1.3 Serious Adverse Event

A serious adverse event or reaction is any untoward medical occurrence 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.)

8.1.4 Expected Serious Adverse Events/Reactions

This clinical trial is being conducted in an acute emergency condition using a drug in common use with a wide safety profile. It is important to consider the natural history of the acute medical event affecting each patient enrolled, the expected complications of this event, and the relevance of the complications to dexamethasone. There are no serious adverse events/reactions expected from the study medication.

8.1.5 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.

8.2 Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study medication as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment (see section 6.6). A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given

appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The relationship of AEs to the study medication will be assessed by a medically qualified investigator.

Any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect.

8.3 Reporting Procedures for Serious Adverse Events

Death, life-threatening complications and prolonged hospital stay are pre-specified outcomes to be reported in this trial. Serious Adverse Events (SAEs) to be reported using an adverse event reporting form will be limited to those NOT already listed as primary or secondary outcomes, but which might reasonably occur as a consequence of the trial drug. If a SAE occurs that does not require immediate reporting, it must be reported to the CI within one working day of discovery or notification of the event (refer to **SOP 11** Adverse Events Monitoring, Reporting and Recording). Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days.

The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants. The Nottingham Clinical Trials Unit (NCTU), who is managing the Trial, will coordinate the reporting all SAEs/SARs/SUSARs to all the relevant Regulatory Agencies, Ethics Committees and local investigators as per local legal requirements.

In addition to the expedited reporting above, the CI, in collaboration with NCTU, shall submit at the end of the trial , or on request, a Safety Report to R&D, the Competent Authority MHRA and Ethics Committee.

9 STATISTICS

A separate detailed statistical analysis plan will be written and “signed off” by the Trial Steering Committee during the set up phase, and will be reviewed annually during hibernation. 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

In a **high severity pandemic,** the **primary outcome measure (proportion admitted to intensive care or died at Day 30)** will be an intention-to-treat analysis using the Chi-square or Fisher's exact test. Death is included in the composite primary outcome (admission to intensive care or death by day 30), and it will also be reported alone as a secondary outcome.

In a **low/moderate severity pandemic,** the **primary outcome measure (length of stay)** will be an intention to treat analysis, using Kaplan Meier plot and log rank test of time to hospital discharge. It is recognised that dying after 5 days in hospital is a very different outcome to going home well after 5 days in hospital. Therefore, a length of stay as 30 days will be assigned for all participants who die (the worst possible as data will be censored at 30 days). The impact of death on length of stay will be assessed by a sensitivity analysis excluding people who died. Death will also be reported as a secondary outcome. In a low severity pandemic it is estimated

that the proportion of deaths is likely to be low (around 2%). In order to allow the trial to report in a timely manner, for the interim analysis, any participant with length of stay in hospital >30 day will be assigned a length of stay of 30 days.

Sub-group analyses will be conducted based on:

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 (defined as any medical illness requiring active regular treatment): underlying co-morbid disease, no underlying co-morbid disease; not known
4) Severity of influenza (severe influenza defined as the presence of 3 or more community triage criteria (Health 2009)): severe influenza; not severe influenza; severity not known.

The treatment effects with respect to the subgroups will be analysed in each subgroup separately as well as in a model with factors for treatment, subgroup and the interaction treatment by subgroup. In this analysis, a Cox-regression model will be used for the time to discharge in the case of a **low/moderate severity pandemic.** In a **high severity pandemic** where death is the primary outcome, a corresponding logistic regression model will be used.

An interim analysis is planned to assess whether early release of results might inform an on-going pandemic. To ensure the trial team remains blinded, the interim analyses will be presented in confidence to a Data Monitoring Committee. It is anticipated that at least one interim analysis will be conducted when 50% of the target sample size has been recruited. The primary interest will be on the primary outcome.

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. The following table presents different scenarios around a 47.5% control event rate.

Sample size calculations for a high severity pandemic

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

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

For a low severity pandemic, a reduction of 20% in length of hospital stay is taken as the minimum clinically relevant change to detect.

Sample size calculations (based on 90% power) in low/moderate severity pandemics

Pandemic severity	Outcome	Effect size	n (per arm)
Low	% change in median LOS	20%	500
Moderate	% change in median LOS	20%	520

LOS: length of hospital stay, ICU: intensive care unit

9.3 The Level of Statistical Significance

The level of statistical significance will be at 5% two-sided, with possible adjustment based on the number of interim analysis. For one interim analysis with 50% of patients' information, the change in the significant level may not be relevant. The statistical analysis plan will contain a detailed consideration of this aspect based on the number of interim analyses

Criteria for the Termination of the Trial

In principle, the interim analysis will be performed to present to the Data Monitoring Committee clinical adverse event data relating to the general safety of patients as criteria for termination of the trial. The primary emphasis will be on death or intensive care admission in the context of a high severity pandemic using Chi-square testing to compare treatment with placebo. Assuming one interim analysis, to stop for safety (i.e. mortality in treatment arm being greater than that in placebo) one requires $p < .025$ from the interim analysis with 50% patients recruited. To stop for benefit (i.e. mortality being less on treatment) one requires $p<0.01$ from the interim analysis.

In a low/moderate severity pandemic, death or intensive care admission will be examined between the two arms using the same criteria for the termination of the trial for safety purposes. To stop for benefit, the criteria will be for length of stay being shorter in the treatment arm with $p<0.01$ using log-rank testing.

These data will be presented to the DMC for consideration. If required, further interim analyses will be performed and criteriae in terms of the p value will be adjusted accordingly. All interim analyses will be performed by a statistician independent of the trial.

9.4 Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be checked for the mechanism of missingness. 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 unused data and spurious data will be queried from the primary source, then the data manager, for further information which will be carefully recorded and presented to the DMC for a collective decision.

9.5 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be described and justified in the protocol if such deviations are identified before publication of the protocol. Otherwise they will be reflected in the final report.

9.6 Inclusion in Analysis

The analysis will be intention to treat. All randomised participants will be included in the analysis.

10 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).

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

12 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.

Regular monitoring will be performed according to ICH GCP. 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 to include an independent chair, two independent members and a patient representative. The TSC will meet to agree the final protocol version, sign off the case report forms and approve the statistical analysis plan prior to any data interrogation. The TSC will meet (either in person or by telephone) annually during the hibernation phase. Crucially, the TSC will be responsible for activating the trial in consultation with the TMG.

An independent Data Monitoring Committee (DMC) will be established to include an independent chair,a disease specific expert and a statistician and will be privy to data as the trial progresses, with a remit of assessing safety outcomes and efficacy outcomes during trial recruitment. The DMC will communicate with the TSC via the nominated trial statistician.

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 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.

13 ETHICS

13.1 Declaration of Helsinki

The CI 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).

13.2 ICH Guidelines for Good Clinical Practice

The CI 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.

13.3 Approvals

The protocol, written consent form, participant information sheet, brief information sheet, postal questionnaire, structured telephone interview and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), 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.

13.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

13.5 Other Ethical Considerations

There are no additional ethical considerations.

14 DATA HANDLING AND RECORD KEEPING

The participants will be identified by a study specific participant's number in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

15 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.

16 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.

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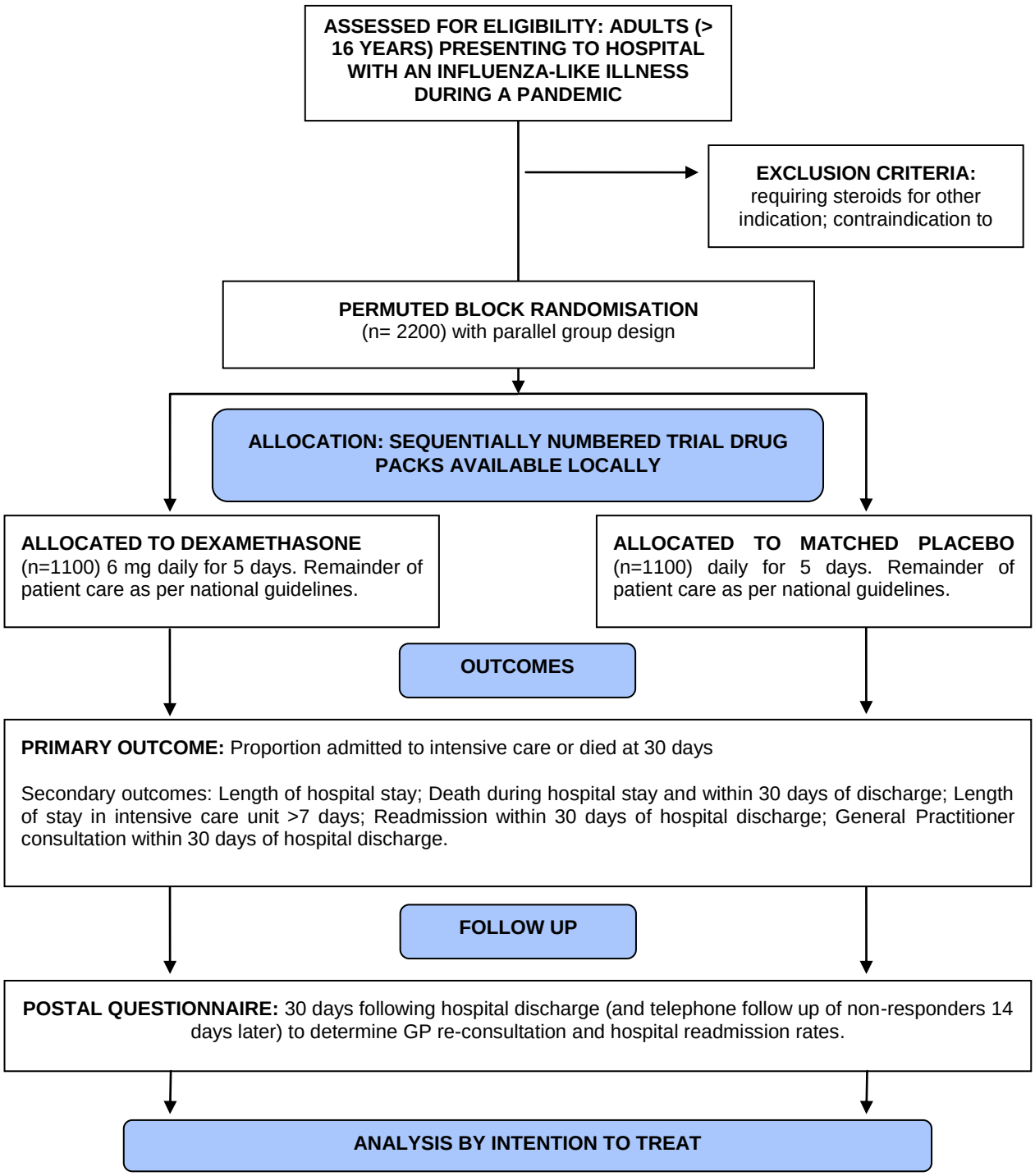
18 APPENDIX A – TRIAL FLOW CHART



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