IMP Management Guidelines for Site Pharmacy and Research Teams

Study Title: *Glu*cocorticoids in adults with *A*cute *R*espiratory *D*istress *S*yndrome: A randomised, parallel-group, allocation-concealed, open label, pragmatic, group sequential design, clinical and cost- effectiveness trial with internal pilot (GuARDS Trial)

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v1	Initial document

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Aim of the trial

The aims of our study are to find out if dexamethasone treatment in patients with ARDS can save lives, reduce the need for extended ICU care, improve longer term patient quality of life and find the best value for the public and health services.

Background

Every year about 120,000 adults who are admitted to Intensive Care Units (ICUs) require a machine, called a ventilator, to help them breathe. In patients who need ventilation, about 1 in 4 have a life-threatening condition with severe breathing difficulties called acute respiratory distress syndrome (ARDS). Unfortunately, around 40% of patients with ARDS die within 60 days of developing this condition.

Breathing difficulties in ARDS happen because the lungs fill with fluid due to inflammation, which is part of the body's response to the conditions causing ARDS. Over the last 30-years, various drug treatments have been tested to reduce the inflammation in ARDS, with little success. At present, there are no drugs that cure ARDS. However, in 2020, a small research study (the DEXA-ARDS trial) in Spain looked at dexamethasone as a treatment for ARDS.

Dexamethasone is a well-known steroid, which is a cheap anti-inflammatory drug that is already widely used to treat other illnesses (such as arthritis and asthma). The result of DEXA-ARDS trial showed that it may help patients survive ARDS. These results from Spain are hopeful but to help us know how effective dexamethasone is, we need to test it in a much larger group of patients who come into the NHS with ARDS. We are planning to conduct a large clinical trial across the UK.

Design of the Trial

The study design is a randomised controlled trial (RCT). We plan to recruit up to 1708 adult patients with ARDS, in approximately 60 ICUs throughout the UK. We will ask patients, or their Legal Representatives if patients are unable to make decisions about their care, to agree (consent) to take part in our study. We will also ask patients if we could follow them up for 6 months after their treatment, as this will give us important information about the clinical effectiveness and cost effectiveness of the treatment. Patients who agree to take part in the trial will then be assigned at random to either dexamethasone in addition to the usual intensive care (intervention), or to usual intensive care only (control), for up to 10 days or until critical care (ICU/HDU) discharge day, whichever occurs first. We will not change other regular care provided in the NHS.

The main outcome of the study is whether dexamethasone improves survival at 60-days compared with usual care.

This study will be open labelled meaning that the healthcare practitioners and patients will know which group of the study they have been allocated to. Blinding is not appropriate in this case as commonly seen side effects of dexamethasone, such as reduced inflammatory markers and raised blood sugar, would point to which group the patient was in.

Investigational Medicinal Product (IMP)

Dexamethasone solution for injection

Prescribed as Dexamethasone (Base) 16.5mg for 5 days and then 8.25mg for 5 days

NOTE: There may be an increased use of dexamethasone in ICU. Ward stock holdings should be maintained to reflect this in accordance with local policy to ensure patients randomised to the intervention can receive the 10 day regimen described in the protocol.

Treatment Arms

- Intervention: Intravenous Dexamethasone for a maximum of 10 days
- Comparator: Usual Care

Dosing

Dexamethasone base 16.5mg on days 1-5 and 8.25mg days 6-10.

Dexamethasone solution for injection can be given without mixing or dilution. When dexamethasone solution for injection is given by intravenous infusion, glucose 5% or sodium chloride 0.9% are recommended as diluents and the infusion should be administered as per local site practice.

No weaning off the dexamethasone dose is required after the 10 days treatment period.

Labelling

The trial has been classified as a Type A risk adapted CTIMP as any potential risk is no higher than that of standard medical care. No specific arrangements are planned for labelling since all dexamethasone injection used in this trial will be licensed medicinal products that are currently commercially available in the UK.

Storage

Storage and supply of the IMP will be undertaken by the site as per the standard local procedures.

Storage conditions for dexamethasone injections should be as per Summary of Product Characteristics (SmPC) for that product. Briefly, Dexamethasone (base) 3.3mg/1mL solution for injection should not be stored above 25°C. Do not freeze. The product should be used immediately after opening but if it is not, it may be refrigerated (2 to 8°C) and used within 24 hours.

Temperature Excursions

As IMP will be taken from local clinical stock, storage monitoring requirements are risk adapted, temperature monitoring will be as per local site practice. No reporting of temperature excursions to the Sponsor is required. It is expected that sites will follow local practice for dealing with temperature excursions in drug storage areas.

Prescribing IMPs

Dexamethasone will be prescribed on the participants' in-patient drug administration chart (or equivalent). All doses given will be recorded on the chart and reasons for a dose being missed will be documented as per routine practice.

Dispensing & Recording

Dexamethasone will be taken from routine clinical stock and dispensed as per local policy. No GuARDS specific dispensing or accountability logs are required.

Batch numbers and expiry details of the ampoules used should be logged as part of the study drug administration pages on the eCRF/database.

Disposal / Destruction

As dexamethasone will be taken from routine clinical stock and only be administered to participants while they are in-patients in ICU there will not be any used or unused IMP returned to site pharmacies. Opened ampoules will be destroyed at ward level. Sites should follow their local practice / policies for drug destruction and documentation. No approval from Sponsor is required.

Recall of IMPs

In the event of a Dexamethasone recall initiated by the manufacturer or Regulatory Authority, site will follow hospital local procedures and must notify the Trial Manager if a study participant has received IMP from affected batches.