DOUBLE-D MAIN TRIAL

Management of adverse events

Early Double sequential Defibrillation in Out of Hospital Cardiac Arrest
- **A Randomized Study**

This randomized trial examines whether giving early double sequential defibrillation — using both anterior–posterior and anterior–lateral pad positions — is more effective than the standard single defibrillation with standard pad placement. The study includes patients with out-of-hospital cardiac arrest who present with an initial shockable rhythm, have already received at least one standard shock, and still require ongoing CPR.

A Randomized Clinical Trial (RCT)
- CIV 25-01-051015

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1. Adverse events, adverse device effects and device deficiencies

1.1. Definitions

1.1.1. *Adverse Event*

An Adverse Event (AE) is untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.
This definition includes events that are anticipated as well as unanticipated events.
This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

1.1.2. *Adverse Device Effect*

An Adverse Device Effect (ADE) is any AE related to the use of an investigational medical device.
This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes both the interventional and comparator.

1.1.3. *Serious Adverse Event*

A Serious Adverse Event (SAE) is any AE that led to any of the following:

a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:
    i. life-threatening illness or injury,
    ii. permanent impairment of a body structure or a body function,
    iii. hospitalization or prolongation of patient hospitalization,
    iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    v. chronic disease,
c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect

1.1.4. *Serious Adverse Device Effect*

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a serious adverse event.
SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device shall not be considered Serious Adverse Device Effects.

1.1.5. *Unanticipated Serious Adverse Device Effect*

An Unanticipated SADE is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a device shall be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not.

SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device shall not be considered Serious Adverse Device Effects.
For the anticipated adverse device effects, se section 4.2 above.

1.1.6. *Device Deficiency*

A Device Deficiency is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.
This includes detected errors at defibrillator self-test after each use.

1.2. Recording and Reporting

1.2.1. *Recording*

As stated in section 13.3 cardiac arrest is associated with a probability of death of 70-80% in the first 30 days. Even among survivors this condition is associated with neurological, cardiac and multi-organ failure in the first post-cardiac arrest period. The standard treatment includes known side effects such as rib-cage fractures and lacerations to visceral organs due to CPR, infections and bleedings associated with invasive ventilation and other procedures during resuscitation and the post cardiac arrest intensive care period. In this population it is difficult, if not impossible, to report all AE and SAE and assess their relation to the intervention.

In this trial, two strategies of defibrillation will be compared but all other treatments will follow standard care. Therefore, adverse events related to the defibrillation process and intervention during resuscitation will be collected with emphasis on device deficiency (DD) and anticipated AE (se section 14.3).

The principal investigator or an authorized designee will record:

- - all AEs and SAEs except the events specified not to be recorded (below)
- - all SADEs;
- - all Device Deficiencies;
- - any new finding in relation to any of the above-mentioned events.

Events that are related to cardiac arrest and would be expected in patients undergoing attempted resuscitation should NOT be reported. These include:

- - Death
- - Hospitalization
- - Persistent or significant disability or incapacity
- - Organ failure
- - Rib fractures and bleeding related to CPR

1.2.2. *Reporting*

The investigators will report all SADEs and Device Deficiencies s to the sponsor, immediately but not later than 3 calendar days after investigation site study personnel's awareness of the event. This includes defibrillation malfunction during use or detected errors at defibrillator self-test after each use.

The sponsor will report to the Swedish Medical Products Agency all of the following reportable events:

- any SADE that has a causal relationship with the investigational device, the comparator or the investigation procedure, or where such causal relationship is reasonably possible;
- any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; and
- any new findings in relation to any event referred to above.

Reporting by the sponsor will be done by filling out the "Summary Reporting Form" (MDCG 2020-10/2). The form will be filled in/updated for each reportable event or for new findings/updates to already reported events. The form will be transmitted to the Swedish Medical Products Agency. For events that indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it will be reported immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. Any other reportable events or a new finding/update to it will be reported immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

1.2.3. *Assessment of Causality*

The relationship between each adverse event and the investigational device, the comparator and the investigation procedure will be assessed and recorded by the investigator and sponsor.

The sponsor and investigator will distinguish between SAEs related to the investigational device and those related to the procedures, relatedness to both is possible.
Each SAE will be classified according to four different levels of causality:

1. Not related
   Relationship to the device, comparator or procedures can be excluded when:
   – the SAE can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

   – the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;

   – the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

   – the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;

– the event involves a body-site or an organ that cannot be affected by the device or procedure;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

2. Possible
   The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained shall also be classified as possible.

3. Probable
   The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship
   The SAE is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
   – the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   – the event has a temporal relationship with investigational device use/application or procedures;
   – the event involves a body-site or organ that
      - the investigational device or procedures are applied to;
      - the investigational device or procedures have an effect on;
   – the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
   – other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
   – harm to the subject is due to error in use;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of the SAE.

1.3. List of foreseeable Adverse events

1. Device deficiency. The inability of one of the defibrillators to deliver energy at defibrillation or shut down / reboot. This risk is judged to be exceedingly low based on the preclinical testing and the results from the previous trials (likely incidence < 1/100). However, it´s impossible to rule out. Defibrillation data will be analyzed for each case and inability to defibrillate will be considered as a SADE. All defibrillator files will be analyzed for energy delivery at each defibrillation.

2. Any device malfunction that becomes evident at defibrillator self-test or test defibrillations performed after each use. There is a theoretical risk that one defibrillator can be damaged by the current delivered from the other device during DSD. Please see also 4.2.

3. Perceived adverse event by participating EMS-units will also be collected in CRF1. All CRF1 forms with perceived adverse events will be followed up by the sponsor with undue delay, the monitor will be informed and the type of adverse event and it´s relationship with the intervention or the investigational device will be judged according to definitions in the CIP.