Standard Operating Procedure 001

Management of intervention group patients

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Scope

- To provide guidance on management of patients who have been allocated to the intervention group in the FLO-ELA Trial.
- The procedures for administering the intervention are described in detail below and a summary is provided on page 6.

Procedure

- The trial intervention period will commence at the start of general anaesthesia and continue for six hours after surgery is complete (maximum total duration: 24 hours).

- In patients already fully sedated and intubated before arrival in the theatre suite, the trial intervention period will commence when the patient arrives in the anaesthetic room / theatre.

Cardiac output monitoring

- Investigators may only use commercially available cardiac output monitoring equipment which displays cardiac stroke volume values and accurately track changes in these values. Suitable technologies are:
    - Arterial pressure waveform analysis (LiDCO Rapid, LiDCO Plus, Edwards Lifesciences EV1000/FloTrac/HemoSphere, Deltex ODM+/TruVue Pulse Pressure Waveform mode)
    - Oesophageal Doppler (Deltex ODM/ODM+/TruVue)

- Immediately following induction of anaesthesia, the selected system will be set up for monitoring of cardiac output. In patients already fully sedated and intubated before arrival for surgery, the selected system should be set up as soon as possible after arrival in the anaesthetic room / theatre.

- If investigators wish to give more than 500ml of fluid boluses in the anaesthetic room / theatre before the induction of anaesthesia, it is recommended that this is guided by cardiac output monitoring.

- Delays in setting up cardiac output monitoring should be avoided and clinicians should aim to use the monitor for at least 80% of the intervention period. Predefined protocol deviations that should be reported are:

    - Failure to use cardiac output monitoring in an intervention group patient
    - Failure to follow the haemodynamic algorithm (defined as at least one cycle of fluid bolus with measurement of stroke volume response) in an intervention group patient when a cardiac output monitor is being used.
    - Use of cardiac output monitoring in a control group patient, including forms of monitoring based on stroke volume variation or pulse pressure variation only.

General haemodynamic measures

Care for all patients has been loosely defined to avoid extremes of clinical practice but also practice misalignment, as follows:

- During the intervention period, patients will receive one of the following fluids at 1 ml/kg/hr as maintenance fluid:
    - 5% dextrose
    - 4% dextrose with 0.18% NaCl (+/- KCl)
    - 5% dextrose with 0.45% NaCl (+/- KCl)

It is recommended that this maintenance fluid is delivered at a fixed rate using an infusion device. Routine maintenance requirements should meet NICE guidance (20-30ml/kg/day of water, approximately 1mmol/kg/day of potassium, sodium and chloride and 50-100g/day of glucose). In certain clinical scenarios such as electrolyte imbalance, an alternative fluid may be selected at the clinician's discretion. For obese patients, the maintenance fluid rate should be adjusted to the ideal body weight (1). A calculator is available within the NELA webtool.

- Blood will be transfused at clinicians' discretion but should maintain haemoglobin at greater than 8 g/dl.

- Oxygen will be administered to achieve a target $Sp0_2$ of ≥94%.

- Core temperature will be maintained between 36.5°C and 37.5°C.

- Mean arterial pressure will be maintained between 60 and 100 mmHg using an alpha adrenoceptor agonist or vasodilator as required. If inotropes, vasoconstrictors or vasodilators are required, they should be provided by intravenous infusion rather than intermittent bolus, as per protocol. Other measures such as adjustments to anaesthesia and analgesia should be considered first.

Post-operative analgesia

- Post-operative analgesia will be provided at the discretion of the clinician in accordance with local protocols.

Administering fluid to a stroke volume end-point

- Currently, peri-operative intra-venous fluid is usually administered to subjective end-points. The use of stroke volume as a treatment end-point may significantly reduce but not eliminate this subjectivity.

- **Stroke volume** and stroke volume **variation** (SVV) will be determined by the cardiac output monitoring system. In order to ensure a standardised approach to fluid administration, no more than 500ml of intra-venous fluid will be administered prior to commencing cardiac output monitoring.

- In addition to the maintenance fluid, patients will receive a 250ml fluid challenge, given over a five minute duration or less, of one of the following solutions:
    - "Balanced" crystalloid: Hartmann's solution (compound sodium lactate, Ringer's lactate), Plasmalyte 148.
    - 0.9% sodium chloride
    - Gelatin-based colloid
    - Albumin

- This fluid challenge will be repeated if there is evidence of fluid responsiveness, defined as ≥10% increase in stroke volume in response to the previous fluid challenge **AND** SVV >5%. This will continue until a maximal value of stroke volume is achieved, defined as a stroke volume maintained for at least 20 minutes with no evidence of fluid responsiveness. In the absence of fluid responsiveness, further fluid challenges are unlikely to be helpful at that time.

- Once the maximal value of stroke volume is determined, this should be maintained with fluid boluses as required. Initial increases in stroke volume are often only transient. If stroke volume does not increase as defined above, it is likely that the heart is functioning on the horizontal part of the Starling curve (see figure). This suggests the patient is not hypovolaemic and fluid challenges should be stopped. If the stroke volume decreases, this is most likely due to ongoing fluid losses and a further fluid challenge is required.

- Many peri-operative physiological changes may alter the maximal value of stroke volume. These may be due to general and regional anaesthesia, surgical stimulation, endotracheal tube removal, pain, fluid loss, etc. Following major changes in haemodynamic status, such as after

emergence from anaesthesia, further 250ml fluid challenge is recommended to re-establish the presence or absence of fluid responsiveness, and the maximal value of stroke volume revised if necessary. The most challenging situation is the patient who clearly remains stroke volume responsive despite large volumes of intra-venous fluid. This arises when an evolving severe fluid deficit has yet to become clinically apparent in any other respect e.g. haemorrhage. Experience from previous trials suggests that it is particularly important to continue to give fluid challenges in such patients to maintain maximal stroke volume. The small volume of each individual fluid challenge will minimise any potential adverse effects of confirming volume status in euvolaemic patients. Data from previous studies confirm the safety of this approach.

- **The measurement of stroke volume does not replace the discretion of the treating clinician in ensuring patient safety. If there is a clear clinical indication, the treating clinician may adjust both the volume and type of fluid administered, e.g. if there is concern about persistent hypovolaemia or fluid overload.** Such decisions may relate to clinical circumstances or physiological measurements (e.g. pulse rate, arterial pressure, urine output, serum lactate, base excess).

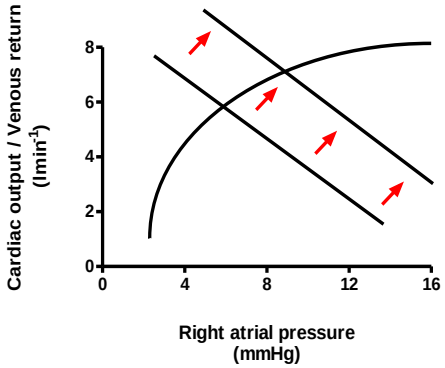


Figure: Starling's curve
The increase in venous return due to intra-venous fluid (red arrows) increases stroke volume in responsive patients. At maximal stroke volume (horizontal part of curve), the absence of a response indicates fluid is not required.

What if blood products or intravenous fluids are required for indications unrelated to changes in stroke volume?

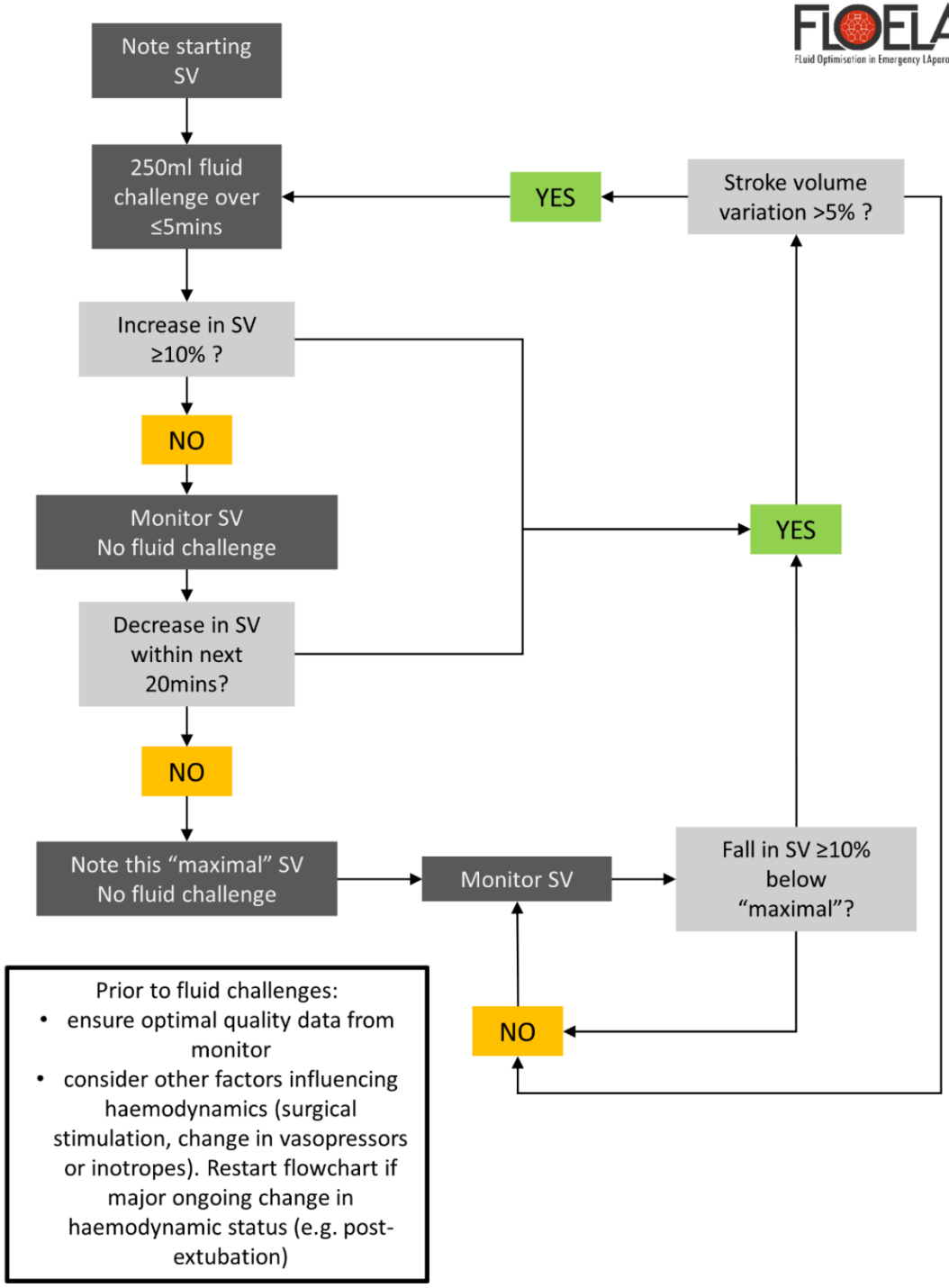
- Many intervention group patients will require blood products and, in some cases, additional intravenous fluid challenges may be requested by a clinician. Administration of fluid, blood or blood products under these circumstances should be performed with stroke volume monitoring and these data should be used to inform the need for subsequent fluid challenges.

Other aspects of care

- All other aspects of care should be in line with local protocols and recommendations on the care of emergency laparotomy patients by the National Emergency Laparotomy Audit (2).

References

1. National Institute of Health and Care Excellence (2017). *Intravenous fluid therapy in adults in hospital (Clinical Guidance 174)*. Available from: https://www.nice.org.uk/guidance/cg174 [Last accessed: 08/08/2018].
2. National Emergency Laparotomy Audit (NELA) project team (2017) *The Third Patient Report of the National Emergency Laparotomy Audit.* Available from: https://www.nela.org.uk/reports?newsid=1047 [Last accessed: 08/08/2018].



General haemodynamic measures (all patients)

1. Maintenance fluid at 1 ml/kg/hr
2. Transfuse blood to maintain haemoglobin >80 g/l
3. Clinician retains discretion to adjust therapy if concerned about risks of hypovolaemia or fluid overload
4. Mean arterial pressure 60-100 mmHg; $Sp0_2$ ≥94%; temperature 36.5 – 37.5°C; heart rate <100 bpm

Document History

Version No.	Date Approved	Reviewer	Details of changes
V1.0	13/08/2017	N/A	N/A
V2.0	16/06/2020	Lucy Johnstone	- Updated model names for approved cardiac output monitoring systems - Correction of Plasmalyte 148 - Correction of predefined protocol deviations. - Stated that inotropes, vasoconstrictors and vasodilators should be given via intravenous infusion (as per protocol). - Updated references