Guidance for the Management of symptoms in adults with Heart Failure at the end of life

This booklet provides guidance to healthcare professionals on managing commonly experienced symptoms for heart failure patients in the last weeks to days of life.
**Management of end stage Heart Failure Symptoms**

This guidance can be used for patients who are still able to take oral (PO) medications but also lists other routes of administration such as sublingual (SL) intravenous (IV), subcutaneous (SC) injection and continuous subcutaneous infusion (CSCI) via syringe pump over 24 hours.

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**Introduction**

This guidance has been developed for healthcare professionals managing heart failure symptoms when end of life is expected within weeks to days. For these patients it would likely be inappropriate to monitor bloods at this stage of a patient’s illness. However due to the trajectory of heart failure it is advised to use clinical judgement to monitor bloods or observations should palliative stage become prolonged or greater than predicted.

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**When it is recognised that a person may be entering end of life:**

- Determine if the patient has an **Implantable Cardioverter Defibrillator (ICD)** and refer to deactivation guidance section below.
- Review and stop any prescribed medication in the last weeks to days of life not providing symptomatic benefit or which may cause harm.
- Discuss and agree any medication changes with the patient and those important to them.
- Ensure onward **referral** to appropriate palliative care support, hospice care and any other local available support services.
- The needs of the patient may be physical, psychological, social, and spiritual or a combination of all of these.
- **Ensure anticipatory medicines have been prescribed by the subcutaneous route SC,** see page 12.

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**ICD (Implantable Cardioverter Defibrillator): Deactivation Advice**

- Shock therapy at end of life is inappropriate and distressing to both patient and family.
- If the patient has an **Implantable Cardioverter Defibrillator (ICD)** discuss with primary consultant cardiologist or consultant on call in regards to deactivating shock therapy.
- While the need for **ICD** deactivation should be discussed early this should be reviewed when planning for end of life care.
- Planned deactivation of an **ICD** can be facilitated at device review clinic if the patient is well enough to attend hospital by contacting your local trust cardiac investigation unit.
- This planned service is available Monday—Friday and during normal working hours.

For emergency **ICD** community deactivation, regardless of location and where adequate planning has not occurred, Belfast Health & Social Care Trust cardiac investigations team should be contacted for further advice.

*All emergency end of life community deactivations are carried out by the Belfast Health & Social Trust within 48 hours.*

**RVH device clinic:** 02890 633179  **BCH device clinic:** 02895 040403

**Out of hours CCU RVH:** 02896 150824 or 02896 150826
# Booklet Contents

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- Medication Advice, pack sizes & anticipatory prescribing table: Pages 10, 11 & 12
- Subcutaneous Furosemide: Page 13
- Helpful tips & advice caring for heart failure patients entering palliative stage: Page 13
- Opioid Conversion Table: Page 14
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The contents of this guidance may differ from other published guidelines, but have been selected to reflect expert opinion, evidence and safety for patients at end of life.

- Users are advised to monitor patients carefully for side effects and response to treatment. Responsibility for the use of these recommendations lies with the healthcare professionals managing each patient.
- Always start with the lowest dose in the range specified in this guide.
- Consider non-pharmacological management of palliative symptoms.

## Heart Failure Specialist Nursing & Palliative Care Teams
- Should you require further advice please contact your local Heart Failure service.
- If the patient is known to Heart Failure service, the patient should hold contact numbers for the local heart failure team or alternatively contact local HSC trust.
- For further palliative care advice please contact the team through the individual hospitals local palliative care team or alternatively contact local hospice in your area.

## Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSCI</td>
<td>continuous subcutaneous infusion</td>
</tr>
<tr>
<td>OD</td>
<td>Once daily</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>DOAC</td>
<td>Direct Oral Anticoagulant</td>
</tr>
<tr>
<td>PO</td>
<td>Oral medicine</td>
</tr>
<tr>
<td>SL</td>
<td>Sublingual</td>
</tr>
<tr>
<td>PRN</td>
<td>As required</td>
</tr>
<tr>
<td>TDS</td>
<td>Three times a daily</td>
</tr>
<tr>
<td>QDS</td>
<td>Four times a day</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>ICD</td>
<td>Implantable Cardiowerter Defibrillator</td>
</tr>
</tbody>
</table>
**Breathlessness**

**Intermittent : tolerating PO medicine**

Consider **Oramorph** 1mg PO 2-4 hourly PRN

Dyspnoea associated with anxiety, consider **Lorazepam** 500 micrograms SL 8 hourly PRN

Consider **Oxygen** 1-2 litre/min via nasal specs PRN if the patient finds this beneficial for symptom management

**Intermittent : Unable to tolerate PO medicine**

Consider **Morphine Sulfate** 1mg-2mg SC 4hrly PRN

If 2 or more doses required in 24 hours consider **Morphine Sulfate** 5mg via **CSCI** and 1mg-2mg SC 4hrly PRN

**Persistent : tolerating PO medicine**

Consider regular **Oramorph** 2mg PO QDS and 2-4 hourly PRN

Dyspnoea associated with anxiety, consider **Lorazepam** 500 micrograms SL 8hrly and if patient tolerating and symptoms persist, consider increasing to 1mg alternatively consider **Diazepam** 2mg-5mg PO 4-6 hourly

**Persistent : Unable to tolerate PO medicines**

Consider **Morphine Sulfate** 5mg via **CSCI** and 1mg-2mg SC 4hrly PRN

If patient is breathless AND anxious, consider:

**Midazolam** 5mg-10mg via **CSCI** over 24 hours and **Midazolam** 2mg SC PRN

**Patients with Severe Chronic Kidney Disease (eGFR <30)** are more susceptible to drug side effects and toxicity, therefore:

1. Consider starting all medications at lowest dose and increase dosing frequency.
2. For **Opioids** consider **Oxycodone** as first line and use conversion table on **page 14** for further guidance.
3. **Alfentanil** may be appropriate in some instances, please seek specialist advice prior to initiating.

**Remember:** For patients commencing opioid medications, consider prescribing regular and/or **PRN** anti-emetic and laxative if appropriate.
Breathlessness & Oedema: Diuretic Therapy

**Tolerating PO medicine**

Consider up titrating oral loop diuretic (e.g., **Bumetanide** 1mg increments or **Furosemide** 40mg increments)

**Consider Thiazide/thiazide-like** diuretic such as **Bendroflumethiazide** 2.5mg – 5mg PO OD or **Metolazone** 2.5mg PO weekly initially, frequency can be increased to 2.5mg alternate days.

If not already on, consider adding or increasing **Spironolactone** 25mg PO alternate days and if tolerated increase to 25mg OD for resistant oedema and breathlessness.

It would likely be inappropriate to monitor bloods at this stage of a patient’s illness.

**Unable to tolerate PO medicines**

Patient unable to swallow oral medicines or persistent symptoms.

**IV access present and available**

Consider **IV Furosemide** bolus using previous **PO** dose as starting dose.

Review after 24 hours and titrate dose if required until symptoms controlled (e.g., **Furosemide** 80mg PO to **Furosemide** 80mg IV).

**IV access lost or inappropriate**

Consider administering **Furosemide** by **CSCI** syringe pump over 24 hours.

Use previous **PO/IV** 24 hour requirement as starting dose for **CSCI** syringe pump and titrate dose as per clinical need (e.g., **Furosemide** 80mg IV/PO to **Furosemide** 80mg via **CSCI**). Review after 24 hours and titrate dose if required until symptoms controlled.

**Furosemide** should not be added to or mixed with other drugs in a **CSCI**.

For further information on the use of **SC Furosemide** please see **page 13**.

Always refer to local trust policy and procedures for use and management of **CSCI**.

**Recommended Infusion Sites:**

- Upper chest and/or upper anterior of arms
  
  (sites are often restricted in heart failure patients due to probable oedema)

- Avoid bony prominences and areas where tissue is damaged, thus decreasing absorption
Nausea

Intermittent: tolerating PO medicine

Consider antiemetic

Metoclopramide 10mgs 6-8 hourly max TID PO PRN

Consider starting a CSCI syringe pump with antiemetic medication

E.g. Metoclopramide 30mg/24 hours

Co-prescribe Levomepromazine 2.5mg—5mg SC PRN 4-6 hourly

Note Metoclopramide and Cyclizine should not be co-prescribed together.
Where possible Cyclizine should be avoided in Heart Failure patients.

Review every 24 hours

Additional Advice:

Ondansetron may be considered as an alternative to the above medications especially in patients with Parkinson’s Disease where Metoclopramide and Levomepromazine may cause extrapyramidal side effects.

Ondansetron can be prescribed 4mg SC 4-6hrly PRN or via CSCI 8mg-24mg over 24 hours.

Ondansetron however is very constipating and this should be considered before prescribing.
Anxiety, delirium and agitation

Assess the patient first to exclude potentially reversible and treatable causes such as infection, urinary retention, severe constipation or drug withdrawal (e.g. nicotine).

**Intermittent: tolerating PO medicine**

Consider

- **Lorazepam** 500 micrograms SL or **Diazepam** 2mg PO PRN 4-6 hourly

**Persistent: tolerating PO medicines**

If symptoms persist consider **Diazepam** 2mg-5mg PO BD or TID

**Intermittent: unable to take PO medicine**

Consider **Midazolam** 2mg-5mg SC 2-4 hourly PRN

If two or more PRN doses required in 24 hours consider prescribing regular **Midazolam** 2mg-5mg by CSCI over 24 hours

**Persistent: Unable to tolerate PO medicines**

Consider **Midazolam** 2mg—5mg by CSCI over 24 hours

AND **Midazolam** 2mg—5mg SC PRN

Re-assess regularly. If symptoms persist add total SC PRN dose over 24 hours to current syringe pump dose (increase breakthrough dose accordingly)

If poor response to increasing dose of **Midazolam** reassess cause of agitation.

Consider stat dose of:

- **Levomepromazine** 5mg-15mg SC
  
  or

- **Haloperidol** 500 micrograms-1mg SC

Assess response and if effective add:

- **Levomepromazine** 10mg—25mg
  
  or

- **Haloperidol** 1mg-3mg by CSCI syringe pump over 24 hours

(Caution: **Haloperidol** is contraindicated with **Metoclopramide**)

(Notes: 1mg-2mg/SC: 1ml syringe 2mg/5ml patient bottle: 0.1ml syringe pump)
Pruritus

Simple measures to aid relief of itch

- Apply moisturiser liberally and often to keep the skin moisturised.
- Simple creams and ointments can be tried, as well as topical corticosteroids.
- Encourage the patient to use warm tepid water for bathing, and to bath less often.
- Consider adding something soothing to the bath, such as sodium bicarbonate or colloidal oatmeal.
- Avoid soaps, shower gels and bubble baths, which dry skin out by washing away natural oils.
- Avoid irritating fabrics. Where possible, cotton and silk can be cooler and less irritating.

First Line

Apply after washing in the morning and again in the evening;

Aqueous cream +/- 1% menthol

Oily calamine lotion +/- 0.5% phenol

Avoid if patients skin is broken.

Second Line

Consider Chlorphenamine 4mg QDS PRN

(max dose 16mgs in 24 hours)

Often pruritus does not resolve with antihistamine therapy.

Please seek specialist advice if necessary and refer to the “Palliative Adult Network Guidelines” Chapter 12 or https://book.pallcare.info
Noisy Respiratory Secretions

Intermittent

Glycopyrronium 200 micrograms SC 4-6 hourly (max dose 1.2mg/24 hours) PRN

Persistent

If two or more PRN doses are required in 24 hours consider

Glycopyrronium 600 micrograms by CSCI syringe pump over 24 hours
AND
Glycopyrronium 200 micrograms SC 4-6 hourly PRN for breakthrough symptoms

If symptoms persist, increase total 24 hour dose to maximum of 1.2mg/24 hours

Review after 24 hours.
If symptoms persist consider changing to:

Hyoscine Butylbromide 120mg by CSCI syringe pump over 24 hours
or
Hyoscine Hydrobromide 2.4mg* by CSCI syringe pump over 24 hours

* Hyoscine Hydrobromide may cause sedation and paradoxical agitation

Review the use of intravenous or subcutaneous fluids and decrease or discontinue if appropriate.
Consider stopping all non-essential medications for patients in the last **weeks** to **days** of life:

Seek advice of heart failure service/cardiology team if necessary.

For renal or hepatic patients seek advice for medicine choice & dose adjustment as required.

<table>
<thead>
<tr>
<th>Consider stopping Medication with only long term benefit</th>
<th>Consider stopping Medication with medium term benefit</th>
<th>Consider stopping Medication with short term benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Angiotension Converting Enzyme inhibitors / Angiotensin Receptor Blockers</td>
<td>Loop &amp; thiazide diuretics</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Beta-blockers</td>
<td>Digoxin/beta-blockers for AF</td>
</tr>
<tr>
<td>Digoxin in patients in sinus rhythm</td>
<td>Spironolactone / Eplerenone</td>
<td></td>
</tr>
<tr>
<td>Anti-anginals e.g. nitrates, nicorandil.</td>
<td>Warfarin/Direct Oral Anticoagulant (DOAC):</td>
<td></td>
</tr>
<tr>
<td><strong>If no recent chest pain or patient hypotensive.</strong></td>
<td>Seek advice for mechanical valve or treatment for Pulmonary Embolism.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clopidogrel, Ticagrelor or other antiplatelet</td>
<td></td>
</tr>
</tbody>
</table>

For further advice on deprescribing, please consult the STOPPFrail Screening Tool Table 1:

https://pure.qub.ac.uk/portal/files/123615482/
STOPPFrail_Consortium_Validation_Accepted_Manuscript.pdf
## Pack size of oral medicines referenced in the policy

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Strength</th>
<th>Pack size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendroflumethiazide</td>
<td>2.5mg tablets</td>
<td>28 tablets</td>
</tr>
<tr>
<td>Chlorphenamine</td>
<td>4mg tablets</td>
<td>28 tablets</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2mg or 5mg tablets</td>
<td>28 tablets</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40mg tablets</td>
<td>28 tablets</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>6mg tablets</td>
<td>10 tablets</td>
</tr>
<tr>
<td>Hyoscine Butylbromide</td>
<td>1mg tablets</td>
<td>28 tablets</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>6mg tablets</td>
<td>10 tablets</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1mg tablets</td>
<td>28 tablets</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10mg tablets</td>
<td>28 tablets</td>
</tr>
</tbody>
</table>
| Metolazone (unlicensed medication) | 5mg tablets | 28 tablets
See BNF for further information | 28 tablets
Available in packs of 50/100 |
| Ondansetron            | 4mg or 8mg                      | 28 tablets |
| Oramorph liquid        | 10mg/5ml liquid                 | 100ml      |
| Spironolactone         | 25mg tablets                    | 28 tablets |

### Injectable

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Strength</th>
<th>Pack Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>10mg/ml in 2ml or 5ml injection</td>
<td>10 ampoules</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>5mg/ml injection</td>
<td>10 ampoules</td>
</tr>
<tr>
<td>Hyoscine Butylbromide</td>
<td>20mg/ml injection</td>
<td>10 ampoules</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>25mg/ml injection</td>
<td>10 ampoules</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>2mg/ml in 2ml or 4ml injection</td>
<td>5 ampoules</td>
</tr>
</tbody>
</table>
Anticipatory Prescribing

Prescribing medicines in anticipation of symptoms that may develop during the last days of life is known as anticipatory prescribing. Having these medicines prescribed and available to the patient can reduce delays in treating symptoms as they develop.

Patients in the last days of life are unlikely to be able to swallow oral medicines and therefore the subcutaneous route is preferred.

Anticipatory medicines should be considered when ICD deactivation occurs if they are not already prescribed.

Below is a list of anticipatory medicines that should be considered to treat the common symptoms that may occur during end of life care in heart failure patients.

The drugs prescribed must however be appropriate to the individual patient.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medicine</th>
<th>SC stat PRN dose</th>
<th>Strength</th>
<th>Pack size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathlessness</td>
<td>Morphine*</td>
<td>1mg-2mg every 4 hours PRN</td>
<td>10mg/ml injection</td>
<td>10 ampoules</td>
</tr>
<tr>
<td>Pain</td>
<td>Morphine*</td>
<td>2mg-5mg every 2-4 hours PRN</td>
<td>10mg/ml injection</td>
<td>10 ampoules</td>
</tr>
<tr>
<td>Anxiety, delirium &amp; agitation</td>
<td>Midazolam</td>
<td>2mg-5mg every 2-4 hours PRN</td>
<td>10mg/2ml injection</td>
<td>10 ampoules</td>
</tr>
<tr>
<td>Noisy respiratory secretions</td>
<td>Glycopyrronium</td>
<td>200micrograms every 4-6 hours PRN</td>
<td>200micrograms/ml injection</td>
<td>10 ampoules</td>
</tr>
<tr>
<td>Nausea</td>
<td>Metoclopramide</td>
<td>10mg every 6-8 hours PRN (max TDS)</td>
<td>10mg/2ml injection</td>
<td>10 ampoules</td>
</tr>
</tbody>
</table>

* Consider oxycodone as first line opioid for those patients with eGFR<30 at equivalent doses using the strength 10mg/ml (pack size =5 ampoules).
Subcutaneous Furosemide

Consideration of the use of subcutaneous Furosemide may be appropriate for patients at palliative stage of heart failure and in the last days to weeks of life who wish to remain at home. These patients may now be unable to take their oral diuretics or their oral diuretics may now be less effective. It would likely be inappropriate to monitor bloods at this stage of a patient’s illness.

- A recent study has suggested that subcutaneous Furosemide has a geometric mean absolute bioavailability of 99.6% and onset of action is 30 minutes.
- Due to the maximum volume of a CSCI being 24ml, the maximum dose of subcutaneous Furosemide that can be given in one CSCI over 24 hours is 240mg (10mg/ml).
- Subcutaneous Furosemide should not be mixed with any other medications in a syringe pump. Furosemide injection is alkaline and should not be mixed or diluted with glucose solutions or other acidic fluids.
- A diluent may not be necessary, but Furosemide can be diluted with sodium chloride 0.9%. If a diluent is required, sodium chloride 0.9% (10ml amps) should be co-prescribed.
- Monitor injection site for signs of reaction and renew as necessary following local trust policy and procedures for the use and management of CSCI.

Dosing guidance

- Use previous PO/IV 24 hour Furosemide requirement as starting dose for CSCI syringe pump and titrate dose as per clinical need
  
  (e.g. Furosemide 80mg IV or PO to Furosemide 80mg via CSCI)

Simple measures when caring for heart failure patients entering the final weeks to days of life:

- Positioning - the most comfortable position is usually sitting upright with support.
- Elevate the patients legs.
- Ensure profiling bed available.
- Keep the room cool.
- Moving air from a fan (hand-held or stationary) or open window as tolerated helps provide psychological relief.
- Careful consideration to oral hygiene as mouth breathing dries the mouth and oxygen (unless humidified) will dry the mouth.
- Consider insertion of self retaining catheter (SRC) especially if on high dose diuretics.
- Where possible stay with patients, this can help alleviate anxiety and agitation.
# Opioid Conversion Table

Refer also to HSC Guidance “Northern Ireland guidelines on converting doses of opioid analgesics for adult use 2018”

## Table 1. Opioid Conversions

<table>
<thead>
<tr>
<th>Conversion</th>
<th>Divisor</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PO (Oral) to PO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Morphine to Oral Oxycodone</td>
<td>Divide by 2</td>
<td>30mg Oral Morphine = 15mg Oral Oxycodone</td>
</tr>
<tr>
<td>Oral Codeine/Dihydrocodeine/Tramadol to Oral Morphine</td>
<td>Divide by 10</td>
<td>240mg Oral Codeine = 24mg Oral Morphine</td>
</tr>
<tr>
<td><strong>PO to SC (Subcutaneous)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Morphine to SC Morphine</td>
<td>Divide by 2</td>
<td>30mg Oral Morphine = 15mg SC Morphine</td>
</tr>
<tr>
<td>Oral Morphine to SC Diamorphine</td>
<td>Divide by 3</td>
<td>30mg Oral Morphine = 10mg SC Diamorphine</td>
</tr>
<tr>
<td>Oral Oxycodone to SC Oxycodone</td>
<td>Divide by 2</td>
<td>10mg Oxycodone = 5mg SC Oxycodone</td>
</tr>
<tr>
<td>Oral Morphine to SC Alfentanil</td>
<td>Divide by 30</td>
<td>30mg Oral Morphine = 1mg SC Alfentanil</td>
</tr>
<tr>
<td><strong>SC (Subcutaneous) to SC Morphine to SC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diamorphine - Divide by 1.5</td>
<td></td>
<td>15mg SC Morphine = 10mg SC Diamorphine</td>
</tr>
<tr>
<td>SC Morphine to SC Oxycodone - Divide by 2</td>
<td></td>
<td>20mg SC Morphine = 10mg SC Oxycodone</td>
</tr>
</tbody>
</table>

*Note this may differ from other available conversions*

## Table 2. Transdermal Patch Conversions

<table>
<thead>
<tr>
<th>Fentanyl Patch eg. Mezolar, Durogesic</th>
<th>Replace patch every 3 DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl Patch (micrograms/hr)</td>
<td>Oral Morphine Dose over 24 hours (mg)</td>
</tr>
<tr>
<td>12</td>
<td>30—59</td>
</tr>
<tr>
<td>25</td>
<td>60—89</td>
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<td>360—419</td>
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<td>175</td>
<td>420—479</td>
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<tr>
<td>200</td>
<td>480—539</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine Patch eg. Butec. BuTrans, Replace every 7DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch Strength (micrograms per hr)</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>20</td>
</tr>
</tbody>
</table>
This guidance ‘Management of symptoms in adults with Heart Failure at the end of life’ has been coproduced and developed through a collaborative network with representation from each HSC Trust.

Utilising expert opinion from Northern Ireland Regional Heart Failure teams, Consultant Cardiologists, Palliative Care, Clinical Physiology, Primary Care & British Heart Foundation Northern Ireland.

- Dr Miriam Johnston, Professor of Palliative Medicine, Dr Tim Hougton, Consultant Cardiologist & Janet Raw Heart Failure Nurse (2012) Guidance for the Prescribing of Subcutaneous Furosemide by Bolus or Syringe Driver for Heart Failure. NHS Bassetlaw & Doncaster. York Teaching Hospital.

- Peter Armstrong & Dr Kiran Kaur (2018) on behalf of the Regional Palliative Care Medicine Group (RPMG) Management of symptoms in adults in the last days.

  Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6059009/

  Available: https://www.nice.org.uk/guidance/ng106

  Available: https://www.nice.org.uk/guidance/ng31

Guidance completed September 2019 - Review date September 2022