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# SWIM (Sickle With Ibuprofen and Morphine) Randomised Controlled Trial Fails To Recruit: Lessons Learned

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| | |

# SWIM (SICKLE WITH IBUPROFEN AND MORPHINE) RANDOMISED CONTROLLED TRIAL FAILS TO RECRUIT: LESSONS LEARNED

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ABSTRACT

**Objectives**

Sickle With Ibuprofen and Morphine (SWIM) Trial was designed to assess whether co-administration of ibuprofen (a non-steroidal anti-inflammatory drug) resulted in a reduction of opioid consumption delivered by patient controlled analgesia (PCA) for acute pain in sickle cell disease.

**Design**

A randomised, placebo-controlled, double-blind trial.

**Setting**

United Kingdom multicentre trial in acute hospital setting.

**Participants**

Adults with sickle cell disease of any gender and phenotype aged 16 years and over.

**Interventions**

Oral ibuprofen at a dose of 800mg three times daily or placebo in addition to opioids (morphine or diamorphine) administered via PCA pump for up to four days.

**Main outcome measures**

The primary outcome measure was opioid consumption over 4 days following randomisation.

**Results**

The SWIM trial closed early because it failed to randomise to its target of 316 patients within a reasonable time.

**Conclusions**

The key issues identified include the unanticipated length of time between informed consent and randomisation, difficulties in randomisation of patients in busy emergency departments, availability of trained staff at weekends and out of hours, fewer than expected hospitals using PCA routinely for sickle cell pain treatment, lack of research staff and support for participation, and trial design. There are implications for future UK funding for trials in sickle cell disease.

**Trial Registration**

ISRCTN Registry Identifier: ISRCTN97241637

ClinicalTrials.gov Identifier: NCT00880373

SUMMARY

**Strengths and limitations of this study**

The SWIM trial was designed as a randomised, placebo controlled, double-blinded trial.

This trial failed to recruit the target number of participants.

## BACKGROUND

Sickle cell disease (SCD) comprises a group of genetic blood disorders that affect over 13,000 people in the UK predominantly of African, Caribbean, Asian, Arabian and Mediterranean origin. The hallmark symptom is pain. Over 50% of patients with sickle cell disease (SCD) admitted to hospital in the UK have acute pain[1], commonly treated with opioids[2] with unpleasant side effects including nausea, constipation, itching, sedation and emotional changes.

Non-Steroidal Anti Inflammatory Drugs (NSAIDs) have been trialled in SCD, and are recommended[3]. However, ketoprofen compared with placebo plus syringe pump administered morphine in SCD failed to demonstrate a morphine sparing effect[4]. Ibuprofen analgesia is dose-related: a single 400mg dose offers one in three patients with moderate to severe pain at least 50% relief (number-needed-to-treat (NNT) of 2.7), compared with placebo; a single 600mg dose provides at least 50% pain relief to one in two patients (NNT of 1.7)[5]. Furthermore, patient controlled analgesia (PCA) using morphine in SCD provides adequate pain relief with reduced opioid consumption compared with continuous infusion[6].

## METHODS

'Sickle With Ibuprofen and Morphine' (SWIM) Trial, the first UK multicentre trial of analgesia in SCD, was a randomised, placebo controlled, double-blinded trial of ibuprofen or placebo, to determine whether ibuprofen could reduce PCA opioid consumption for acute SCD pain.

The National Research Ethics Service, and Medicines and Healthcare products Regulatory Agency approved the SWIM trial.

**Participants and Recruitment**

Participants were adults (aged 16 years and over) with SCD of any phenotype, admitted to hospital with acute SCD pain for which opioids were warranted. Exclusions were: contraindications to morphine, diamorphine, or ibuprofen including peptic ulcers and NSAID induced asthma; renal dysfunction; stroke in preceding 6 weeks; pregnancy or breastfeeding.

Recruitment was in two stages:

1. Screening, informed consent and trial registration in outpatient clinics
2. Verbal assent and randomisation in Emergency Departments (A&E) on admission for SCD pain requiring opioid analgesia

Sample size calculation assumed a mean opioid consumption in the control group of 33mg (sd 43) over 4 days[6]. To detect a 50% reduction (90% power, 5% significance), required 286 patients; the recruitment target of 316 (158 per arm) allowed for 10% attrition.

Patients were randomised (1:1) to oral ibuprofen 800mg three times daily, or matching placebo, in addition to morphine or diamorphine via PCA for a maximum of 4 days during hospitalisation. Randomisation used permuted blocks stratified by centre; each patient was randomised only once by assigning the patient to the next available treatment pack number with the allocation sequence generated by the MRC Clinical Trials Unit.

The primary outcome was opioid consumption over 4 days.

RESULTS

Daily pain and symptom scores were recorded over the 4 days (Table 1). Treatment effects and 95% confidence intervals were calculated using an unadjusted linear regression model.

The SWIM trial was terminated early because of very slow randomisation. Patients were recruited over 16 months, 83 consented to the trial but only 7 patients were randomised

(Figure 1). Two main issues emerged at closure. Firstly, although the number of registered patients increased steadily, there was often a long delay between consent and randomisation. Secondly, there was not sufficient participation from SCD centres; 27 were approached, 5 did not respond, 12 declined, 10 expressed interest, 4 registered patients, and only 2 sites randomised patients.

## DISCUSSION

Several contributory factors for early closure of the SWIM trial, and potential remedies were identified:

1. Monitoring of emergency admissions for SCD pain at the lead trial site found that 11 registered patients were not randomised because they presented at A&E during weekends or at night when no SWIM trial trained staff were present. Good Clinical Practice (GCP) training of A&E staff performing randomisation was challenging due to high staff turnover. A SWIM trial specific GCP training package was developed, which was easier to deliver on a more frequent basis. Nevertheless, there was insufficient time for this to have an impact on randomisation.
2. A&E at the lead site was closed overnight for a significant proportion of the study due to low staffing levels and safety concerns. Therefore, some registered patients were admitted to other hospitals. A system to allow randomisation of a registered patient admitted at a different site was planned which would have improved the randomisation rate.
3. A SWIM trial protocol amendment to allow randomisation for repeated admissions had been approved by the trial oversight committees but not implemented before closure[7].
4. The SWIM trial was adopted onto the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio. Nonetheless, initiation of trial sites was slow and research support was difficult to access. Several interested centres could not participate because they did not use opioid PCA. Other reasons included lack of research infrastructure, and anticipated difficulties with randomisation in busy A&Es.
5. Many SCD patients did not have frequent hospitalisations, with a longer than anticipated delay between consent and randomisation, although it was encouraging that only 25% of eligible patients declined to participate.

The SWIM trial was conducted within the UK National Health Service (NHS), and was unsuccessful mainly due to lack of interest or capacity at several large SCD centres, overestimation of the number of eligible patients, and unanticipated long delays between registration and randomisation. USA SCD trials also failed to recruit[8-10]. Explanations cited include complex protocol design, insufficient staff, lack of research support, time constraints of clinical staff, requirement for trained staff at weekends and out of hours, involvement of multiple departments, and fewer than expected eligible or consenting patients. These reasons are similar to the SWIM trial; nonetheless specific strategies have to be adopted in the UK which has a different health service structure and no strong culture of SCD research to encourage successful participation.

There is a clinical need for research to improve treatment and outcomes in SCD in the NHS, nonetheless there is no SCD research network. The NIHR CRN portfolio provides funding, however this is based on patients randomised, rather than patients consented. In addition, CRN research capacity funds are usually awarded competitively based on research activity. Therefore, research inactive SCD centres are unlikely to be awarded funds for staff or capacity building to enable participation in trials such as SWIM. Unless these issues are addressed SCD trials in the UK will continue to fail.

ACKNOWLEDGEMENTS

The trial was funded by the Health Technology Assessment (HTA) Programme of the National Institute of Health Research (NIHR) in the UK (Grant No. 07/48/01), and sponsored by London North West Healthcare NHS Trust.

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AUTHORS CONTRIBUTION

The SWIM trial was a collaborative effort between NHS Trusts and the MRC Clinical Trials Unit. Gavin Cho was the chief investigator. Kofi Anie, Mark Layton, and Claire Hemmaway were co-principal investigators. Jacky Buckton was the trial coordinator, Patricia Kiilu, Lydia Alexander, and Dorothy Sutton were involved in patient recruitment. Claire Amos was the project manager, Caroline Dore and Brennan Kahan were trial statisticians. Sarah Meredith was the head of clinical operations. Kofi Anie took the lead in the write up with contributions, review and editing by the other authors.

COMPETING INTERESTS

The authors have no competing interests.

The corresponding author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that there are not any discrepancies from the study as planned.

LICENCE AGREEMENT

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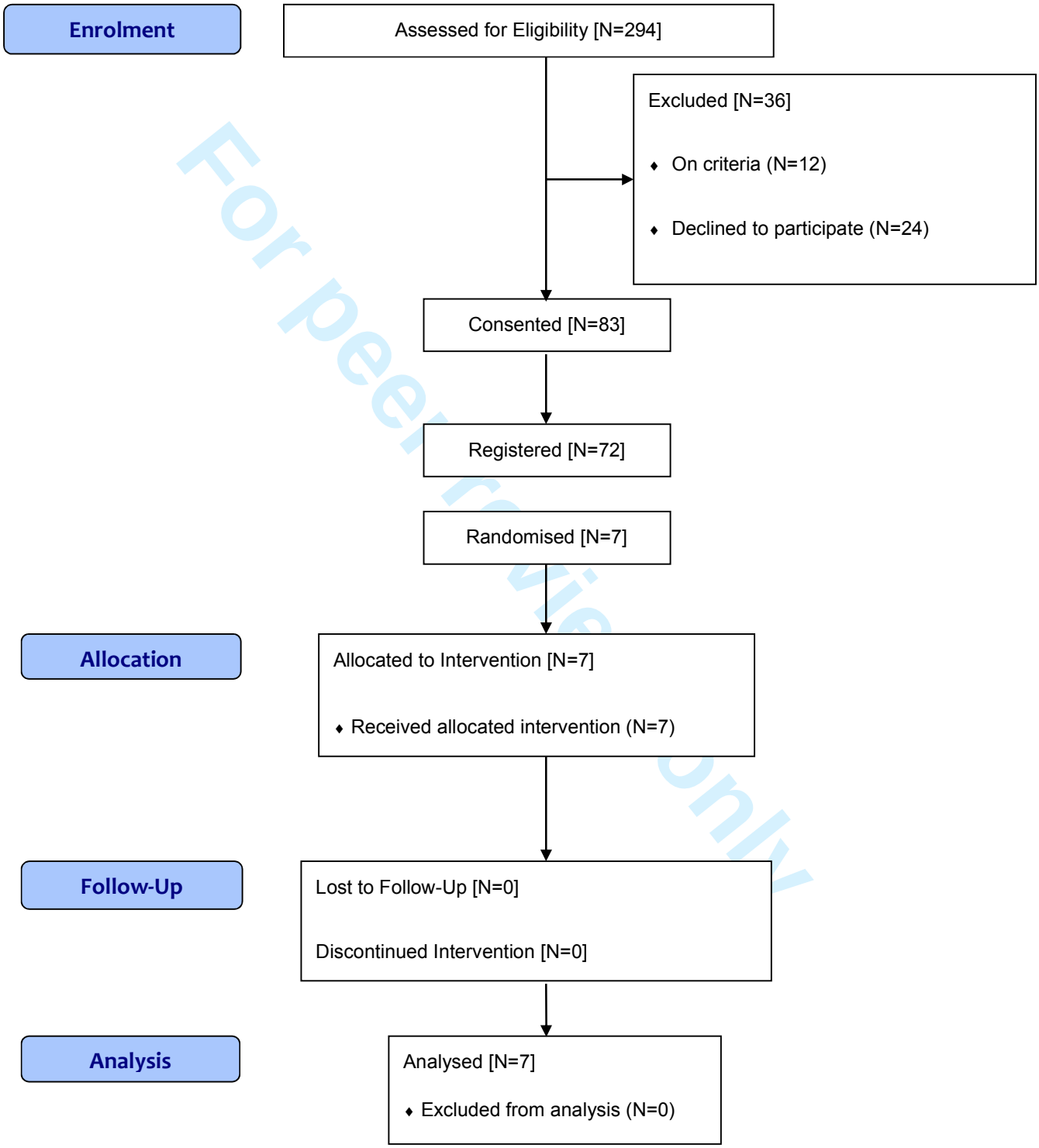
**Table 1: Clinical outcomes for each treatment arm**

| | Ibuprofen (n=2) | Placebo (n=5) | Difference in means (Ibuprofen vs. placebo) (95% CI) |
|---|---|---|---|
| Opioid consumption over 4 days (mg) – mean (SD) | 110 (45) | 206 (104) | -96 (-301 to 109) |
| Pain score over 4 days* – mean (SD) | 1.5 (0.7) | 3.2 (1.4) | -1.7 (-4.4 to 1.1) |
| Number of self-reported side effects per patient** (mild , moderate, or severe) – mean (SD) | 7.5 (0.7) | 10.2 (2.2) | -2.7 (-6.9 to 1.5) |
| Number of self-reported side effects per patient** (severe) – mean (SD) | 3.0 (1.4) | 3.2 (3.1) | -0.2 (-6.3 to 5.9) |

*Pain scores were measured using a 10 point scale (0 to 10) with higher scores indicating more pain.

**Self-reported side effects included nausea, vomiting, diarrhoea, constipation, stomach pain/discomfort, blood in stool, mood/emotional changes, sleep disturbances, dizziness, headache, itching, dry mouth, sore chest, and breathing difficulties, and each symptom was graded as none, mild, moderate, or severe.

**Figure 1: Patient recruitment at SWIM Trial Closure**




# SWIM

(**S**ickle **W**ith **I**buprofen & **M**orphine)

# An evaluation of the effectiveness of ibuprofen and morphine / diamorphine for acute pain in sickle cell disease

## A multi-centre, double-blind , placebo-controlled randomised trial

**SWIM TRIAL CLINICAL PROTOCOL**
**VERSION: Draft protocol version v 4.0**
**RELEASE DATE: 7 October 2010**

**PROTOCOL NUMBER: HTA 07/48/01**
**ISRCTN97241637**
**EUDRACT NUMBER: 2008-006846-24**
**MHRA CTA: 13045/0005/001-001**

| **Authorised by:** | | | |
|---|---|---|---|
| **Name:** | **Dr Gavin Cho** | **Role:** | **Chief Investigator** |
| Signature: | | Date: | 7 October 2010 |
| **Name:** | **Caroline Doré** | **Role:** | **CTU Project Lead** |
| Signature: | | Date: | 7 October 2010 |

## General Information

This document describes the SWIM trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the SWIM Trial Manager, MRC Clinical Trials Unit, London to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Principal Investigator.

- **Compliance**

  The SWIM trial will be conducted in compliance with the protocol, Principles of GCP, Data Protection Act (DPA number: Z5886415), NHS research governance and The Medicines for Human Use (Clinical Trials) Regulations, as appropriate.

- **Sponsor**

  North West London Hospitals NHS Trust
  Research and Development
  Northwick Park Hospital
  Watford Road
  Harrow
  Middlesex
  HA1 3UJ
  Tel: 020 8869 2011
  Fax: 020 8869 5218

- **Funder**

  NIHR Health Technology Assessment Programme

| | | |
|---|---|---|
| | **SAE NOTIFICATION** | |
| | Within one working day of becoming aware of an SAE, please fax a completed SAE form to the MRC Clinical Trials Unit on: | |
| | **Fax: 020 7670 4818** | |

# TRIAL PERSONNEL AND CONTACT DETAILS

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Consultant Haematologist

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Consultant Psychologist

**Dr Mark Layton**
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## ABBREVIATIONS AND GLOSSARY

| | |
|---|---|
| **AE** | Adverse Event |
| **A&E** | Accident and Emergency |
| **ALT** | Alanine Aminotransferase |
| **AR** | Adverse Reaction |
| **AUC** | Area Under the Curve |
| **CF** | Consent Form |
| **CI** | Chief Investigator |
| **CKD** | Chronic Kidney Disease |
| **CRF** | Case Report Form |
| **CRP** | C-reactive Protein |
| **CTA** | Clinical Trials Authorisation |
| **CTU** | Clinical Trials Unit |
| **DCF** | Data Clarification Form |
| **DMC** | Data Monitoring Committee |
| **eGFR** | Estimated Glomerular Filtration Rate |
| **EUDRACT** | European Union Drug Regulatory Agency for Clinical Trials |
| **GCP** | Good Clinical Practice |
| **GFR** | Glomerular Filtration Rate |
| **HADS** | Hospital Anxiety and Depression Scale |
| **Hb** | Haemoglobin |
| **HbS** | Sickle Haemoglobin |
| **HE** | Health Economics |
| **IB** | Investigator's Brochure |
| **IDMC** | Independent Data Monitoring Committee |
| **ISRCTN** | International Standard Randomised Controlled Trial Number |
| **LDH** | Lactate Dehydrogenase |
| **LFTs** | Liver Function Tests |
| **MCH** | Mean Corpuscular Haemoglobin |
| **MCV** | Mean Corpuscular Volume |
| **MDRD** | Modification of Diet in Renal Disease |
| **Mg** | Milligrams |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **MRC** | Medical Research Council |
| **MRC CTU** | Medical Research Council Clinical Trials Unit |
| **NHS** | National Health Service |
| **NSAID** | Non-Steroidal Anti-Inflammatory Drug |
| **PCA** | Patient Controlled Analgesia |
| **PI** | Principal Investigator |
| **PIS** | Patient Information Sheet |
| **QA** | Quality Assurance |
| **QC** | Quality Control |
| **QL** | Quality of Life |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SCD** | Sickle Cell Disease |
| **SD** | Standard Deviation |
| **SOP** | Standard Operating Procedures |
| **SPC** | Summary of Product Characteristics |
| **SSA** | Site Specific Assessment |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |

| | |
|---|---|
| **SWIM** | Sickle With Ibuprofen and Morphine |
| **TMG** | Trial Management Group |
| **TMT** | Trial Management Team |
| **TSC** | Trial Steering Committee |
| **TSF** | Trial Site File |
| **UAR** | Unexpected Adverse Reaction |
| **WBC** | White Blood Cell |

# 1. SUMMARY

## 1.1 Abstract and summary of trial design

### 1.1.1 Type of design

SWIM is a multi-centre, double-blind, placebo-controlled randomised trial.

### 1.1.2 Disease/patients studied

In the SWIM trial, the target population is adult patients (aged 16 years and over) with Sickle Cell Disease (SCD) of any phenotype, admitted to hospital with acute sickle cell pain crisis for which the prescription of opioids is warranted. The study will be introduced to potentially eligible patients in the Sickle Cell or Haematology Outpatient Clinics and consent sought. If they are subsequently admitted to hospital with an acute pain episode they will be asked whether they still wish to participate prior to randomisation. For more details refer to section 4.

### 1.1.3 Trial interventions – research and control

The **current treatment** used during a hospital admission for an acute sickle cell pain crisis is opioid-based analgesia, frequently administered via a pump by patient controlled analgesia (PCA). However, opioids have many side effects including nausea, constipation, itching and emotional changes. Better ways to manage sickle cell pain are required which will reduce the amount of opioids used, thus reducing side-effects while maintaining or improving pain relief.

In the **SWIM Trial**, we will assess whether co-administration of ibuprofen (a non-steroidal anti-inflammatory drug), which is a non-opioid analgesic, will result in patients requiring less opioid delivered by PCA over a four day period. All patients will be given an opioid (either morphine or diamorphine) via PCA, and, in addition, oral ibuprofen or placebo, will be taken at a dose of 800mg three times daily for up to four days. Ibuprofen is one of the most widely used NSAIDs for pain relief and has a clear dose-related analgesic response. Its selection for this trial is based on dose, safety, and costs.[1] Most importantly, the risk of gastrointestinal complications with ibuprofen is lower than other NSAIDs.[2]

For more details refer to Section 7.

### 1.1.4 Outcome measures

The primary outcome measure will be opioid consumption over four days following randomisation.

Secondary outcome measures include:

- Pain scores measured using a ten point ordinal scale
- Time to achieve a pain score of four on a ten-point ordinal scale
- Sickle pain patient assessment
- Unsuccessful pain control requiring alternative analgesia
- Quality of life and utility (EQ-5D)
- Hospital Anxiety and Depression Scale (HADS)
- Patient satisfaction

- Sickle cell complications and treatment
- Adverse effects (safety)
- Duration of admission
- Readmission to hospital (safety)

For more details refer to Section 9.2.

### 1.1.5 Duration

Each patient will be participating in the trial from randomisation at the start of the index admission to 4 weeks following hospital discharge. After the 4 (or less) days in-hospital treatment period, the patient will continue to be monitored by telephone one week after discharge and at a clinic visit 4 weeks after discharge.

For more details refer to Sections 7.1 and 8.1.

### 1.1.6 Data recorded directly on CRFs

Usually, data will be recorded on case report forms (CRFs). The top copy/original should be sent to the MRC CTU for data entry and a copy kept at the local centre. A list of CRFs can be viewed in Appendix 1. The type of data to be recorded is detailed in the Treatment Data Collection (Section 7.7).

### 1.1.7 Ancillary studies/sub-studies

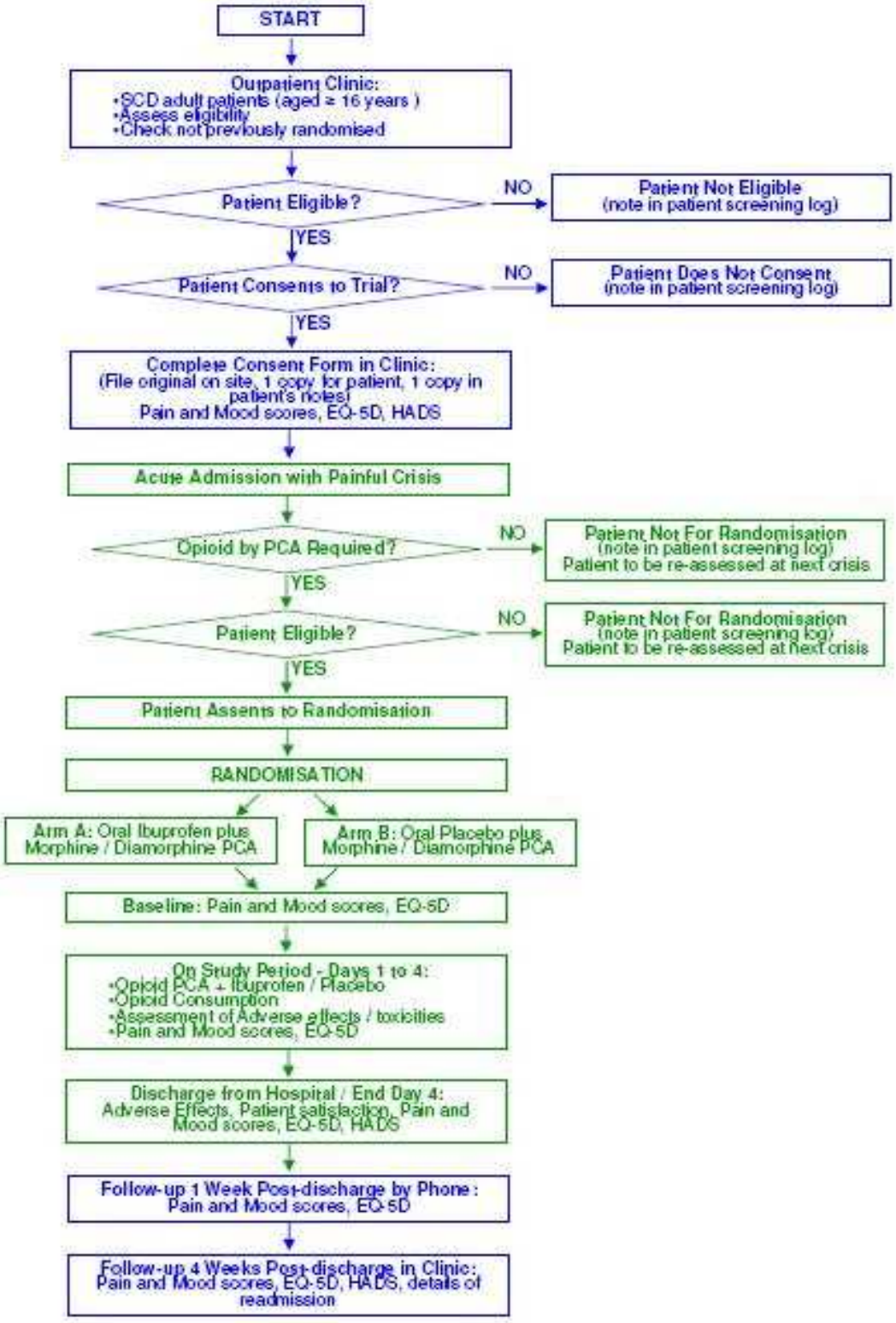
No formal ancillary studies / sub-studies are being conducted.

### 1.1.8 Organisation

The North West London Hospitals NHS Trust is the sponsor of the SWIM trial and trial co-ordination is being carried out by the Medical Research Council (MRC) Clinical Trials Unit (CTU). The NIHR Health Technology Assessment Programme is funding the trial.

## 1.2 Flow diagram

**Figure 1: Trial entry, randomisation and treatment**



# 2. BACKGROUND

## 2.1 Introduction

### 2.1.1 Relevant studies/trials

Sickle cell disease (SCD) is an inherited abnormality of the haemoglobin protein in red blood cells. People with sickle cell disease have red blood cells that contain mostly haemoglobin-S, an abnormal type of haemoglobin. Sometimes these red blood cells become sickle-shaped (crescent shaped) and have difficulty passing through small blood vessels.

In people who inherit one copy of the gene there is some protection against falciparium malaria, while inheritance of the sickle haemoglobin (HbS) gene from both parents or HbS with another variant haemoglobin gene (e.g. HbC, HbβThalassaemia) gives rise to clinical problems. The symptoms of SCD are anaemia, infection and the consequences of blood vessel blockage (vaso-occlusion). The latter deprives tissues of oxygen and is the cause of the acute pain crises, the hallmark of SCD, and other clinical syndromes such as stroke, chest complications including pulmonary hypertension, priapism, leg ulcer and chronic organ failure.

The type of pain is highly variable both within and among patients, and is the result of complex and poorly understood interactions between biological and psychosocial factors. Vaso-occlusion within the bone marrow vasculature leads to bone infarction, which in turn results in the release of inflammatory mediators that activate afferent nerve fibres and cause pain. Although the basic mechanism is simple, the precise details of the vaso-occlusion are poorly understood, involving complex interactions between red cells, endothelium, white cells and platelets. The unpredictability of the pain is a major factor in undermining the patient's ability to cope.[3]

SCD is a global health problem. In the UK, it predominantly affects people of African and Caribbean origin, and those from Asia, Arabia, and the Mediterranean, with about 170 affected babies being born annually.[4] SCD often has a major impact on school attendance, education and employment thus aggravating any socio-economic disadvantages.

To date, treatment is based on supportive measures. Blood transfusions are used for severe anaemia and prevention of strokes, and to suppress the production of sickle haemoglobin. Antibiotic prophylaxis is used to prevent infections, especially in children, and oxygen is utilised in treating patients with acute chest syndrome.[5,6] Other measures may be effective for managing sickle cell crises such as the application of heat and massage to improve circulation. Bone marrow transplantation can prevent, stabilise or reverse the onset of complications associated with sickle cell disease.[7] A few patients have been cured by stem-cell transplantation, however problems of age restrictions, and the difficulty of finding suitable donors would continue to limit its application. Hydroxyurea has been found to raise the level of foetal haemoglobin (HbF) and decrease cellular dehydration. Thus, this therapy is very effective in preventing and reducing the rate of painful episodes and the subsequent number of hospitalisations experienced by patients.[8]

Even with optimal management, most people with SCD experience painful crises.[9] Most SCD pain episodes are acute, and can vary from short transient attacks of 5 to 10 minutes, to severe generalised pain lasting days or weeks.[10] The frequency of painful crises varies widely, some individuals experience pain on a daily to weekly basis, while others have an episode

once every few months or years. Recurrent acute episodes are persistent throughout life for which frequent hospitalisations may be required.[11,12]

SCD pain is treated with analgesia and hydration. Pain control is usually in progressive stages and requires a variety of medications: mild pain is treated with oral non-opioid analgesics such as paracetamol or aspirin; moderate pain is treated with weak oral opioids such as codeine, dyhydrocodeine, or co-proxamol; severe pain in the hospital setting is managed aggressively with parenteral opioids such as morphine or pethidine.[3] However, the use of opioids continues to pose a challenge to clinicians.[13,14] Also, the level of opioid use for SCD in the community seems to be related to mood changes and not necessarily due to severe pain.[15]

SCD has a significant impact on health services usage, for example data from the Department of Health showed that 87% of hospital consultant episodes for SCD in England required hospital admission; 62% of these were emergency admissions.[16] This impact of SCD has led to the implementation of the universal NHS Screening programme for all newborns since 2004.

Opioids are widely accepted as the treatment of choice for severe acute pain in SCD, however clinical trials in its use alone and with other analgesics are limited. Some studies have compared the use of opioids in addition to NSAIDs (mainly parenteral ketorelac) or placebo, and measured opioid consumption.[17,18,19,20] These studies broadly suggest that NSAIDs may lead to a reduction of opioid consumption. Others have compared NSAIDs with opioids showing the benefits of parenteral ketorelac over pethidine[21] or oral opioids with parenteral opioids revealing no differences.[22] All these studies were conducted in the USA, and generally with small numbers of patients. To date there have been no clinical trials of any analgesics for SCD pain crisis in the UK. A Cochrane Systematic Review suggested that regular NSAIDs should be considered for acute SCD pain crises.[23] However, this recommendation is based on work in other areas of acute pain.[1]

There is no clear evidence for the effectiveness of oral NSAIDs in combination with parenteral opioids via PCA in adults with SCD. Also, there is only one randomised controlled trial in SCD conducted in the Netherlands. This study showed that treating SCD patients with morphine via patient controlled analgesia (PCA) on hospital admission results in adequate pain relief with lower consumption when compared with patients treated with continuous infusion.[2]

### 2.1.2 Population

The target population is adult patients (aged 16 years and over) with Sickle Cell Disease (SCD) of any phenotype, admitted to hospital with acute sickle cell pain crisis for which the prescription of opioids is warranted. The study would be introduced to potentially eligible patients in the Sickle Cell or Haematology Outpatient Clinics and consent sought. If they are subsequently admitted to hospital with an acute pain episode they would be re-consented prior to randomisation.

### 2.1.3 Investigational product/ intervention(s)

Ibuprofen is one of the most widely used NSAIDs and has the best safety profile. Ibuprofen has prominent anti-inflammatory, antipyretic and analgesic effects, which are both peripheral and central.

This protocol outlines a randomised double-blind controlled trial to evaluate the effectiveness of oral ibuprofen in addition to parenteral opioid via PCA.

## 2.2 Rationale and objectives

SWIM is a randomised double-blind controlled trial to evaluate the effectiveness of oral ibuprofen plus opioid via PCA. The results will provide the evidence needed to recommend whether or not ibuprofen should be used in addition to opioid PCA to treat painful crisis associated with SCD.

The formal list of outcome measures is presented in Section 9.2.

### 2.2.1 Risks and benefits

Opioids are commonly used for management of acute painful crises in SCD, however they are associated with a long list of side-effects. Finding an effective adjunct to opioids, which could reduce the amount of opioid required during a stay in hospital, would be of benefit to patients in terms of reduced opioid-induced side-effects without an increase in overall side-effects, while maintaining or improving pain relief.

There is no clear evidence for the effectiveness of oral NSAIDs in combination with parenteral opioids in adults with SCD. Previous research in acute pain suggests that in single doses for postoperative pain the choice between ibuprofen and other NSAIDs seems to be based on dose, safety, and costs.[24] Ibuprofen is cheaper and more importantly the risk of gastrointestinal complications as a result of multiple doses is lower than with other NSAIDs.[25]

There is a clear dose-related analgesic response with ibuprofen and a single dose of 400mg offers one out of every three patients with pain of moderate to severe intensity at least 50% pain relief (number-needed-to-treat i.e. NNT of 2.7), which they would not have achieved with placebo. At 600mg one out of every two patients (NNT of 1.7) has at least 50% pain relief.[24]

### 2.2.2 Objectives

The main objectives of the SWIM Trial of oral ibuprofen combined with opioid administered through PCA for acute pain crisis in adults with sickle cell disease are to:

1. Reduce the use of opioids
2. Assess the clinical effectiveness
3. Improve overall satisfaction with the hospital admission
4. Assess the cost effectiveness

# 3. SELECTION OF CENTRES/CLINICIANS

## 3.1 Centre/Clinician inclusion criteria

1. A pre-requisite to a centre participating in this trial is that it currently uses, or is willing to use, PCA for patients admitted for acute pain in SCD
2. The centre uses either morphine or diamorphine in its PCA protocol.
3. The PCA protocol must have been approved by the NHS Trust
4. The centre has an adequate number of experienced staff to conduct the trial properly and safely according to GCP i.e. to be able to be trained to follow the treatment protocol required and record all of the assessments at the appropriate times as described in Sections 7. and 8.
5. The centre has a reasonable number of SCD patients within its catchment area who will fulfil the patient inclusion criteria listed in Section 4.
6. The clinician involved in treating the SCD patients has an interest in research into this disease and is prepared to take on the role of Principal Investigator
7. The centre will be able to arrange a system for notifying A&E and inpatient ward staff that a patient who presents acutely and has already signed a consent form should be randomised into the SWIM trial (verbal assent should also be obtained)
8. The centre is able to provide estimated GFR (eGFR) results quickly and out-of-hours
9. A&E staff willing to obtain verbal assent and to randomise patients into the trial
10. The centre is able to ensure that all CRFs are completed as per protocol requirements (including out-of-hours and on weekends)

# 4. SELECTION OF PATIENTS

## 4.1 Patient inclusion criteria

### 4.1.1 At time of Consent (in clinic)

1. Adult patients of any gender with SCD of any phenotype (confirmed by HB electrophoresis, DNA analysis or HPLC)
2. Aged at least 16 years
3. Willing to be asked for verbal assent during the next acute pain crisis admission

### 4.1.2 At time of Randomisation

1. Suffering from acute sickle crisis
2. Previously signed SWIM trial consent form at admitting hospital

## 4.2 Patient exclusion criteria

### 4.2.1 At time of Consent (in clinic)

1. Patient has a history of allergic reaction to either morphine / diamorphine or ibuprofen
2. Patient has contraindications to morphine / diamorphine or ibuprofen e.g. Peptic ulcer disease, NSAID-induced asthma
3. Patient receiving drug treatment with which opioids or NSAIDs are likely to interact significantly
4. Patient is in a drug-dependency programme
5. Stage 1 – 5 chronic kidney disease (ref Appendix 2), including urine protein: creatinine ratio of >50 *
6. Patient is on renal dialysis
7. Stroke within the last 6 weeks
8. Platelet count <50 x $10^9$/l
9. Oxygen saturation by pulse oximetry <94%
10. Patient is pregnant or breastfeeding
11. Doctor unwilling to randomise the patient for other reasons
12. Previous randomisation in the SWIM trial
13. Participation in another clinical trial within the last month

* Because the ibuprofen dose is substantial it is felt that precautions should be taken to exclude those who have any signs of chronic kidney disease. One of the signs of kidney disease is “persistent proteinuria”. Therefore, the patient who intermittently has proteinuria (which could be due to other reasons) could still participate.

### 4.2.2 At time of Randomisation

1. Points 1 – 13 listed in 4.2.1 above
2. Consent form not signed
3. Reduction of >10% in eGFR between consent and randomisation

## 4.3 Number and source of patients

Based on the sample size calculation 316 patients will be recruited. Patients will be recruited through North West London hospitals, which are part of the Managed Clinical Network for Haemoglobinopathies, and in other hospitals inside and outside the London area.

# 5. PRE-RANDOMISATION SCREENING PROCEDURES AND CONSENT

When patients attend their out-patient clinic appointment, they will be told about the trial and given the Patient Information Sheet to read. Once this is done and the patient has agreed to participate in the trial, the **informed consent form** will be personally signed and dated by the patient **and** by the person who obtained the informed consent. Copies of the signed consent form will be given to the patient and placed in the patient's medical notes and the original kept in the Trial Site File (TSF). The **Screening Log** must be completed for all screened patients (irrespective of eligibility). All patients must provide written informed consent before any trial specific procedures are performed.

The following screening tests will then be done:

Routine blood tests

- Full Blood Count (Hb, WBC, Platelets, MCH, MCV)
- LFTs (ALT, Alkaline phosphatase, bilirubin)
- CRP
- LDH
- Urea, Creatinine, Sodium, Potassium, estimated GFR* (eGFR)

*If your laboratory cannot readily provide an eGFR result, please calculate it using the abbreviated MDRD equation.

**Abbreviated MDRD equation**

**eGFR** = 186 x (Creat / 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black)

If you have an eGFR value calculated by a local laboratory, use that as it is likely to be more accurate than this calculator, which cannot take into account local variations in creatinine measurements."

A useful website for calculating eGFR is **http://www.renal.org/eGFRcalc/GFR.pl**

Other tests:

- Urine protein:creatinine ratio
- Pulse Oximetry

At this point, the **Registration Form CRF** should be completed if patient is eligble, comprising of:

- Sickle cell characteristics
- Eligibility criteria
- Baseline/steady-state clinical parameters

A letter will be sent to the patient's GP to inform them of the patient's involvement in the trial if a patient agrees.

Each centre will establish a system for notifying A&E and inpatient ward staff that a patient who presents acutely has consented to participate in the SWIM trial and for eligible patients to be randomised and treated. Methods which could be used include a set of specific folders for

these patients, or a marker in the general hospital notes. In addition, patients will be given a patient ID card to carry and they will be asked to show this card to staff in A&E.

# 6. RANDOMISATION & ENROLMENT PROCEDURE

## 6.1 Randomisation practicalities

When patients present acutely, they will be assessed and if their sickle cell pain is severe enough to require hospital admission and a PCA opioid pump, they will undergo investigations to confirm eligibility.

Routine blood tests to be done during an acute assessment include those that form part of the exclusion criteria (e.g. platelet count and creatinine / eGFR). **The eGFR measured during the acute assessment should not be more than 10% lower than the level measured at registration.**

The blood results should be obtained as quickly as possible as they must be checked before randomisation into the trial can take place. All inclusion and exclusion criteria must be satisfied prior to randomisation. Only eligible participants will be randomised.

Patients will be reminded of their previous consent and asked if they still wish to participate in the trial. If the patient assents, the eligibility criteria will be checked again to ensure that they are still eligible to enter the trial and they will then be randomised into the trial. If a patient is ineligible at this stage the randomisation form showing the reason they were not randomised should be retained for your records and a copy should be sent / faxed to the MRC CTU.

Randomisation will be done by assigning the patient to the next available pack number on the **Randomisation Log,** which will correspond to a number on one of the trial packs. Ensure that the patient's pack number on the Randomisation Log and trial pack are identical. The patient's randomisation into the SWIM trial should then be recorded in the patient's hospital notes and onto the **Randomisation CRF**

The patient must be randomised into the SWIM trial preferably within 2 hours (but no more than 4 hours) after starting the opioid PCA pump. At the time of randomisation into the SWIM trial, the **Randomisation CRF** should be completed. Complete the eligibility section before randomisation takes place, and check that the patient has signed an informed consent form (forms should be easily accessible to A&E staff) and that they have been asked whether they still wish to participate in the trial. The completed form must be sent by post / fax to the SWIM trial manager at the MRC CTU as soon after randomisation as possible.

Following randomisation, the **Admission details and Baseline Characteristics CRF** must be completed. This form details the patient's medical history and recent medication usage on admission. It will also record current test results as listed below:

- Full Blood Count (Hb, WBC, Platelets, MCH, MCV)
- Urea, Creatinine, Sodium, Potassium, estimated GFR
- LFTs (ALT, Alkaline phosphatase, bilirubin)
- CRP
- LDH
- Pulse Oximetry

Further details on the method of randomisation can be found in section 9.1.

## 6.2 Randomisation codes and unblinding

While the safety of patients in the SWIM trial should always take priority, maintenance of blinding is crucial to the integrity of the trial. Unblinding is strongly discouraged during treatment and should only be undertaken if the knowledge of whether the patient has been allocated to ibuprofen or placebo is clearly essential for, and will alter, the appropriate medical management of the patient. If a Principal Investigator does wish to unblind a particular patient, it should be discussed with one of the clinical members of the Trial Management Group who is not involved in the care of that patient.

Only one of the trial statisticians should unblind the patient (not the trial manager – reasons of maintaining blinding), and inform the local investigator, **only** after consultation with and authorisation from the Chief Investigator or clinical member of the Trial Management Group. All instances of unblinding and the reason for it should be reported, in writing, to the SWIM Trial Manager at the MRC CTU.

CTU staff who are not involved in the day-to-day running of the trial would be responsible for unblinding possible SUSARs and notification to regulatory authorities.

# 7. TREATMENT OF PATIENTS

## 7.1 Trial treatment

Before randomisation, a PCA pump will be attached to each patient which will dispense the opioid subcutaneously or intravenously in accordance with the individual hospital's protocol for management of acute sickle cell crisis. Clinicians should take into account patient's previous opioid requirements.

Preferably within 2 hours (but no more than 4 hours) after starting the PCA pump and when blood results have confirmed the patient's eligibility for the trial, patients will be randomised between:

- Arm A: opioid PCA with oral ibuprofen
- Arm B: opioid PCA with oral placebo

Ibuprofen 200mg/placebo will be offered orally at a dose of 4 capsules (total 800mg) three times daily for a maximum of 4 days. The initial dose should be given just after randomisation preferably within 2 hours of starting the opioid PCA pump.

**The first dose of oral therapy will be taken just after randomisation when the PCA is started and, thereafter, approximately every 8 hours e.g. 6:00am, 2:00pm and 10:00pm (to tie in with regular drug rounds) until a maximum of 12 doses have been taken.**

**If patients come off their PCA pump for any reason before 4 days has elapsed, they may continue to take oral ibuprofen/placebo until discharge or for a total of 4 days**.

Patients who are finding that their pain is well managed should be encouraged to continue taking their oral therapy and to have less opioid, rather than reducing the dose of oral therapy.

The PCA pump will remain in situ for as long as the patient requires morphine/diamorphine, and the background infusion rate /bolus size will be adjusted as necessary to control the patient's pain. Morphine/diamorphine consumption will be recorded for a maximum of four days. If the patient wishes to come off PCA for any reason, ibuprofen/placebo will continue to be offered three times daily for up to four days post randomisation provided he/she remains in hospital. Within the four day post-randomisation period, PCA may be started again if required and opioid consumption will continue to be recorded. If the patient leaves hospital before four days, the opioid consumption up to that point will be recorded, on the assumption that for the remaining time, opioid consumption is zero. During the admission, some patients may require additional doses of parenteral opioid on top of that received via PCA. Any extra ad hoc doses of opioid given parenterally during the four day post-randomisation period will be recorded and included in the overall opioid consumption data. If the patient is still on PCA after 4 days, ibuprofen/placebo administration will stop and opioid consumption data collection will also stop but the patient will continue with whatever medication is necessary for treatment of their painful crisis.

Refer to section 8.1 below for the follow-up schedule.

## 7.2 Trial product(s)

The opioid (morphine or diamorphine) will be supplied by the participating centre's pharmacy as stock as part of the acute care of sickle cell patients. Controlled drugs regulations must be adhered to at all times.

Converted diamorphine may be used in some centres, with equianalgesia conversion assumed to be 3 to 2 (morphine to diamorphine).

Ibuprofen (Boots 200mg caplets) and placebo will be supplied by Bilcare GCS Ltd.

Each 48 capsule finished product trial drug pack will contain either:

- 48 plain white size 1 capsules containing over-encapsulated ibuprofen 200mg caplets, back filled with microcrystalline cellulose (Arm A)
- 48 matching placebo plain white size 1 capsules containing microcrystalline cellulose in the same proportions as in the active capsules (Arm

B) Each dose will consist of 4 capsules.

Each 48 capsule pack will be:

- labelled in accordance with legal and regulatory requirements
- labelled with a unique medication pack number to maintain blinding

The finished products will be stored centrally at Bilcare GCS Ltd. Bilcare will transfer supplies to participating sites upon request by the sponsor.

## 7.3 Dispensing

Each hospital pharmacy will keep an agreed upon minimum number of packs of trial medication. The pharmacy will initially issue a specified number of trial packs to the clinical area (A&E or ward depending on where randomisation will take place). The clinical area should always keep a set minimum number of trial packs in a specified, locked and temperature monitored cupboard. When a pack is used for a patient it is the responsibility of the principal investigator or nominated delegate to inform pharmacy of the dispensing. A replacement pack will then be issued to the clinical area.

## 7.4 Modification of trial treatment

Interruption or discontinuation of SWIM trial treatment remains the responsibility of the treating consultant and should be done in accordance with standard local practice. It is recommended that treatment is discontinued in the following circumstances:

Opioids should be discontinued if the patient suffers from a clinically significant episode of:

- Respiratory depression
- Hypotension
- Hallucination
- Confusion
- Urinary retention
- Brachycardia
- Tachycardia
- Hypersensitivity reaction

Ibuprofen should be discontinued if the patient suffers from a clinically significant episode of:

- Hypersensitivity reaction
- GI discomfort uncontrolled by a proton pump inhibitor
- GI bleeding
- Haematuria (macroscopic)
- Renal Failure

All dose modifications, discontinued treatment and severe side effects / toxicities should be recorded on the **PCA CRF**. All serious adverse events should be recorded on the **SAE and Notable Event form**. Any SAEs that occur between the time of randomisation into the trial and the 4 weeks post-discharge clinic visit should be recorded and reported to the SWIM Trial Manager (refer to Section 11. ).

## 7.5 Accountability and unused drugs

Both analgesic products used in the SWIM trial are in widespread clinical use and are licensed for the treatment of acute pain. Opioids will therefore be dispensed and administered by ward staff in the same manner as other drugs and there will not be any additional drug accountability procedures other than what is routinely practiced in the ward.

For morphine/diamorphine: When changing PCA bags or syringes, please retain the used PCA delivery system until all details have been recorded in the patient's notes and on the **PCA CRF**.

For ibuprofen/placebo: The following is a guide and may vary from one centre to another

- When packs from Bilcare are received by the pharmacy they must be logged in a master drug accountability log (or something similar) in sequential pack number.
- When the next sequential pack is issued to a clinical area by pharmacy the date of issue and the quantity supplied should be documented on the master drug accountability log.
- When the next sequential pack is dispensed to a patient a patient drug accountability log (or something similar) should be completed by the doctor/nurse.
- This log must be returned to pharmacy at the next available opportunity.
- A member of pharmacy should reconcile the master drug accountability log with the information from the patient drug accountability log.
- Pharmacy will then issue a replacement pack (the next sequential pack) to the clinical area.
- Both logs will then be filed in the appropriate section of the specific clinical trial pharmacy folder.
- All used packs (either empty or not) must be retained by nursing/medical staff and returned to pharmacy to complete a final accountability check.
- Any unused ibuprofen/placebo must be returned to the pharmacy in its original packaging.

## 7.6 Measures of compliance

The opioid PCA does not require a measure of compliance.

For the ibuprofen / placebo, it will be assumed that the patient has taken the medication if the nursing staff have dispensed the medication and provided a signature on the patient's drugs chart to confirm this.

If the prescribing begins in A&E then the drug chart will follow the patient to the required ward. The nursing staff will administer the ibuprofen / placebo at the times specified in Section 6.1. Treatment will continue for the full four days only if required and then be stopped.

Compliance will be audited by completion of the trial forms and validation of the patient drugs charts.

## 7.7 Treatment data collection

The following trial data will be collected at the frequency described for each. The date and time each set of data are recorded will be noted. The trial data and frequency of collection are also summarised in a table shown in Section 8.

- **Assessment of own health state CRF**, comprising:
  - **Pain:** Patients score their level of pain on a scale of 0-10.
  - **Mood:** This consists of a series of two questions about the patient's mood and alertness/drowsiness.
  - **EQ-5D**[26]**:** This is an established self-assessed generic measure of quality of life and consists of five questions about the patient's health state on the day the questionnaire is completed. It also includes an overall score (0-100) that the patient applies to their health state that day.

  This form is to be completed:
  - pre-trial in outpatient clinic when giving consent
  - at baseline i.e. on admission and randomisation to the trial
  - daily for up to 4 days throughout the treatment period or until discharge (whichever is shorter). These forms should be completed at roughly 24 hour intervals, preferably together with the morning drugs round.
  - one week after discharge, via the telephone
  - 4 weeks after discharge at the clinic visit

- **Hospital Anxiety and Depression Scale (HADS)**. This is an established self-assessed questionnaire which measures anxiety and depression felt during the past week. To be completed pre-trial at outpatient clinic when giving consent, Day 4 post randomisation or discharge (whichever is sooner) and then 4 weeks after discharge.

- **Admission details and baseline parameters**, comprising:
  - Admission details
  - Clinical Parameters

  To be completed as soon after randomisation as possible.

- **SWIM Treatment Form**:
  - **Morphine / diamorphine consumption by PCA** – to include any extra opioid administered parenterally during the four day post-randomisation trial period

    Recommended method to record 24 hour opiate consumption accurately:

    PCA bags or syringes should be changed every 24 hours and data read from the machine and recorded

    If this is not possible, read and record data after 24 hours and then zero the PCA machine

    If this is not possible, opiate consumption should be recorded at the end of each 24 hour period

    Retain used bags or syringes (for verification purposes)
  - **Ibuprofen/placebo consumption**
  - **Sickle cell complications and treatment.** Any relevant notes about any clinical developments and/or treatment relevant to SCD which occur from the point of randomisation until discharge will be recorded, including any transfusions.
  - **Pain Score:** Patients score their level of pain on a scale of 0-10. During their stay as an in-patient, pain scores are routinely recorded throughout the day, and this practice will continue as normal. For the trial data, individual pain scores will be recorded on the Daily Pain Score Form.

- **Serious Adverse Events** will be recorded on an **SAE CRF** whenever they occur (i.e. during the patient's stay in hospital and until the 4 week post-discharge clinic visit.).

- **Withdrawal and discharge** details.

- **Re-admission to hospital.** Dates and duration of any readmissions during the 4 week period post discharge will be noted.

## 7.8 Non-trial treatment

### 7.8.1 Medications permitted

The use of non-SWIM trial analgesia (including other opioids and NSAIDS) during the first four days following randomisation is discouraged. If other analgesics are required then they need to be appropriately recorded. Participants in the trial may receive all other normal treatment (e.g. proton pump inhibitors or antibiotics). Please check all other medications to ensure that the patient does not receive any drugs with significant interactions with opioids or NSAIDs.

Woman who are pregnant or breastfeeding are excluded from the SWIM trial.

### 7.8.2 Data on concomitant medication

All other analgesia will be recorded from the point of arrival at hospital until discharge.

## 7.9 Co-enrolment guidelines

There are other clinical trials ongoing for patients with sickle cell disease. Patients cannot be randomised into the SWIM trial if they are already participating in another clinical trial or have participated in another clinical trial in the last month. After admission and randomisation to

the SWIM trial, the patient should not participate in any other clinical trial involving analgesics until after the one-month period following discharge.

## 7.10 Early stopping of trial intervention

By providing consent to be randomised in the SWIM trial, patients are agreeing to SWIM trial treatment, trial follow-up and data collection. If a patient wishes to discontinue trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes.

Patients may stop trial treatment for any of the following reasons:

- Patient withdraws consent
- Illness which prevents treatment
- Any change in the patient's condition which justifies a change in treatment plan
- A serious adverse event has occurred that is at least possibly attributable to ibuprofen and the attending physician decides to stop trial-treatment

Discontinuation of trial treatment must be recorded on the **Discharge CRF**.

Patients who did not receive any of the allocated trial intervention (ibuprofen or placebo) after randomisation will be excluded from the intention to treat analysis. Every effort will be made to collect follow up data on all randomised patients including those who discontinue the trial intervention.

# 8. ASSESSMENTS AND FOLLOW-UP

## 8.1 Schedule for follow-up

**Table 1: Table of Assessments**

| Assessment | In clinic when giving consent pre-trial | On Admission / Baseline | Day 1, Day 2, Day 3 | Day 4 | Discharge | 1 week post discharge (phone) | 4 weeks post discharge (clinic) | Comments |
|---|---|---|---|---|---|---|---|---|
| Assessment of Own Health State (Pain and Mood, EQ-5D) | √ | √ | √* | √* | √ | √ | √ | * Pain score collected as many times as necessary. |
| Hospital Anxiety and Depression Scale (HADS) | √ | | | √# | √# | | √ | #Day 4 **or** discharge, whichever is earlier |
| Baseline blood and other clinical parameters | √ | √ | | | | | | |
| Opioid consumption via PCA and parenteral ad-hoc doses | | | √ | √ | | | | |
| Ibuprofen / placebo consumption | | | √ | √ | | | | Record time of administration |
| Additional medication (analgesia and others) | | | √ | √ | | | | |
| Adverse effects | | | √ | √ | | √ | √ | SAEs, SARS, SUSARS recorded until 4 weeks post discharge |
| Sickle cell complications and treatment | | | √ | √ | | √ | √ | Include transfusions given while in hospital |
| Readmission to hospital | | | | | | √ | √ | Record dates of any readmission during the 4 weeks post discharge |
| Arrange 1week post-discharge telephone call and 4 weeks post-discharge clinic visit | | | | | √ | | | |

**Table 2: Table of Assessments According to Stage of Trial**

| In clinic at time of consent | Admission for painful crisis: randomisation | Treatment period: Day 1 - 4 | Discharge | 1 week post-discharge (via phone) | 4 weeks post-discharge (in clinic) |
|---|---|---|---|---|---|
| **Informed consent:**<br>□ Patient Information Sheet<br>□ Signed Consent Form<br>□ Patient Wallet Card<br><br>**SWIM Registration CRF:**<br>□ Eligibility / exclusion checklist<br>□ Blood and other clinical parameters<br><br>**Assessment of Own Health State CRF**[1]<br><br>**Hospital Anxiety and Depression Scale (HADS)** | **SWIM Randomisation CRF** including eligibility / exclusion checklist<br><br>**SWIM Admission Details and Baseline Characteristics CRF:**<br>□ Admission details<br>□ Patient history<br>□ Blood and other clinical parameters<br><br>**Assessment of Own Health State CRF**[1] | **SWIM Treatment CRFs:**<br>□ Opioid consumption via PCA<br>□ Ibuprofen / placebo consumption<br>□ Additional analgesia<br>□ Sickle cell complications and treatment (including details of transfusions if given)<br>□ Adverse effects<br><br>**Daily Pain Scores**[2]<br><br>**SAE CRF** if applicable<br><br>**Assessment of Own Health State CRF**[1]<br><br>Day 4 only: **HADS**[3] | **Discharge details**<br><br>**Assessment of Own Health State CRF**[1]<br><br>**Reminder of post discharge follow-up:** arrange 1week post-discharge telephone call and 4 weeks post-discharge clinic visit | **Assessment of Own Health State CRF**[1]<br>□ Patient Satisfaction<br><br>Readmission to hospital? Details if applicable<br><br>**SAE CRF** if applicable | **Assessment of Own Health State CRF**[1]<br>□ Further sickle cell complications and treatment required<br><br>Readmission to hospital? Details if applicable<br><br>**SAE CRF** if applicable<br><br>**HADS** |
| Each form is numbered. Please refer to the lists below to see which forms should be completed at each milestone: | | | | | |
| Forms to complete:<br><br>1<br>2 (self-assessed) HADS | Forms to complete:<br><br>3<br>4 (self-assessed)<br>5 | Forms to complete:<br><br>**Day 1:** 6, 7 (self-assessed)<br>**Day 2:** 8, 9 (self-assessed)<br>**Day 3:** 10, 11 (self-assessed)<br>**Day 4:** 12, 13 (self-assessed), HADS[3]<br><br>**14** (daily pain scores)<br><br>19 (SAE form) as Required | Forms to complete:<br><br>□ 15, 16 | Forms to complete:<br><br>17<br>19 (SAE form) as required | Forms to complete:<br><br>18<br>19 (SAE form) as Required<br><br>HADS |

[1] Incorporates Pain and Mood Scores and EQ-5D [2] Pain scores collected as many times as necessary
[3] Collected on Day 4 or at discharge – whichever is earlier

## 8.2 Procedures for assessing efficacy

Efficacy as measured by the primary outcome measure will be assessed by the total amount of opioid consumed during the first four days following randomisation. The changes in pain score over time will also be used to assess efficacy.

If a patient comes off the PCA pump before 4 days but is still in pain, which needs to be controlled by an alternative form of analgesia, this will be recorded as 'unsuccessful pain control'. This data should be recorded on the appropriate **Treatment CRF** and if applicable on the **One week** or **4 weeks post-discharge CRFs**.

## 8.3 Procedures for assessing safety

Safety parameters and procedures will include the following assessments:

- Solicited adverse events associated with opioid and ibuprofen side-effects
- Clinical examination
- SAE / SAR reporting
    - All non-serious AEs/ARs, whether expected or not, should be recorded in the toxicity section of the **PCA Form** and sent to the MRC CTU within one month of the form being due.
    - SAEs/SARs should be notified to the MRC CTU as described in Section 11. All serious adverse events should be recorded on the **SAE form**. Any SAEs that occur from the time of randomisation into the trial until the 4 weeks post-discharge clinic visit should be recorded and reported to the SWIM Trial Manager. The Chief Investigator or other medically qualified delegates will review all SAE reports received.
- Laboratory evaluations
- Sickle cell complications and treatment

## 8.4 Other assessments

**Assessment of Own Health State CRF** must be completed by the patient at the specified time points (see Section 7.7). Questionnaires should be completed without conferring with friends or relatives and all questions should be answered even if the patient feels them to be irrelevant. The appointed person at the site should check each questionnaire for its completeness, ensuring that the correct date of completion and patient identifiers are present.

## 8.5 Patient transfers

For patients moving from the original admitting hospital, every effort should be made to arrange for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient. A copy of the patient CRFs will need to be provided to the new site. The patient would have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre.

## 8.6 Early stopping of follow-up

If a patient explicitly states their wish not to contribute further data to the study, the MRC CTU should be informed in writing of the patient's decision and a **discontinuation form** completed. Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial and data up to this time can be included in the trial if it is anonymised/made anonymous.

# 9. STATISTICAL CONSIDERATIONS

## 9.1 Method of Randomisation

Treatment will be allocated by randomisation. To promote balanced baseline patient characteristics across the treatment groups, randomisation will be stratified using random permuted blocks within centre.

## 9.2 Outcome Measures

### 9.2.1 Primary

The primary outcome measure in the SWIM trial is total opioid consumed in milligrams (mg) during the first four days following randomisation (or until discharge if earlier than four days). Converted diamorphine may be used in some centres, with equianalgesia conversion assumed to be 3 to 2 (morphine to diamorphine).

### 9.2.2 Secondary

The secondary outcomes are:

- Effects on rapidity of pain control – time to achieve a pain score of 4 on a standard 10-point numeric rating score within 4 days.
- Changes in mood – measured on the Hospital Anxiety and Depression Scale (HADS).
- Occurrence of adverse opioid effects – including nausea, constipation, itching and central nervous system effects.
- Effects on occurrence and frequency of other sickle cell complications – including neurological events and acute chest syndrome.
- Number of blood transfusions required prior to discharge.
- Health Service Utilisation Cost – length of hospital admission and any re-admission during 30 days post-discharge.
- Effects on Quality of Life and Utility – measured on the EuroQoL (EQ-5D).
- Effects on patient satisfaction – assessed at discharge.

## 9.3 Sample Size

The mean morphine consumption over four days in the control group is assumed to be 33mg (SD 43).[23] To detect a 50% reduction in morphine consumption over four days with 90% power and using 5% significance level, 286 patients are required. Assuming a 10% rate of dropout or missing primary outcome data 316 patients should be recruited (158 per arm).

As the estimate of the standard deviation of the primary outcome measure in the control group is not reliable (based on 12 patients[23]), the sample size will be recalculated after the primary outcome has been obtained on the first 100 patients. This will be done without breaking the treatment allocation code.[27] The Data Monitoring Committee will be asked for advice on any modification to the total sample size.

After randomisation to the study has finished and the final 4 weeks post-discharge follow up visit has taken place, data cleaning will be completed within three months of the final follow up visit, and statistical analysis will be completed within three months of database lock.

## 9.4 Interim Monitoring and Analyses

There are no formal interim analyses built into the trial design. The Data Monitoring Committee will review efficacy and safety data by treatment group. There are no built in stopping guidelines for efficacy.

## 9.5 Analysis Plan (brief)

### 9.5.1 Primary Outcomes

The primary outcome is measured on a continuous scale (mg morphine consumed). It may be of value to transform this so that analytical assumptions are reasonable (e.g. normality of residuals).

The primary analysis will compare mean morphine consumption (or some transformation of morphine consumption) between the ibuprofen and placebo groups. The analysis will be adjusted for centre effects.

This is a pragmatic trial so the analysis will be done on the basis of (modified) intention-to-treat. Any patient who is randomised and dispensed study drug will have their data analysed, regardless of whether they take the drug. If patients withdraw from study treatment, their data will be used and they will continue to be followed up. If patients withdraw consent for the study, data collected up until that point will be included in analyses, provided they do not direct that they wish for all data collected to be removed from the database. The only exception to this principle is when the patient is randomised but not dispensed study drug. This is not foreseen, but should the situation arise there is no way that omitting these patients from the analysis could introduce bias.

Missing data on the primary outcome are not anticipated since this will be collected entirely during a patient's hospital stay. In cases where the patient leaves hospital before the four days are finished it will be assumed that pain has reduced sufficiently that subsequent morphine consumption would be zero had they stayed in hospital.

### 9.5.2 Secondary Outcomes

Secondary outcomes for efficacy are often collected at more than one timepoint over the duration of hospital stay. The strategy for each of these outcomes is to calculate the area under the outcome-time response curve (AUC) for each patient. Mean AUC will be compared across the two treatment groups. This strategy assumes that all post discharge scores would have been zero if the patient was discharged before four days.

There will inevitably be missing data on secondary outcomes – particularly where the patient is reporting the data. In these cases, multiple imputation will be used to obtain valid inferences under the missing at random assumption.

For safety outcomes, the proportion of patients with an event will be compared between the treatment groups. The Data Monitoring Committee will see this information at regular intervals as the trial progresses.

A detailed statistical analysis plan will be developed prior to the final analysis and will be a separate document.

# 10. TRIAL MONITORING

## 10.1 Risk assessment

The MRC CTU has performed a risk assessment to assess the impact of trial participation on the rights and safety of participants, the reliability of trial results and on the impact of trial results on the research institution leading the trial. The risk assessment has been discussed and approved by the MRC CTU Quality Management Committee. The risk assessment is stored independently of this document.

The outcome of this assessment has been used to guide the development of procedures with respect to informed consent, confidentiality, trial monitoring and audit.

## 10.2 Monitoring at MRC CTU

The MRC CTU will conduct central monitoring of the trial as described in the SWIM Quality Management and Monitoring Plan.

In terms of data, compliance and accuracy will also be routinely monitored by trial management staff at the MRC CTU.

- Compliance: MRC CTU will send regular reminders for any overdue and missing data.
- Accuracy: Data stored at MRC CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, a photocopy of the problematic CRF(s) will be returned to the local site by post or fax for checking and confirmation or correction, as appropriate – any data which are changed should be crossed through with a single line and initialled and dated. The amended version should be returned to MRC CTU and the site's copy should also be amended.

## 10.3 Clinical site monitoring

### 10.3.1 Direct Access to Data

Participating centres must agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data/documents as required. Patients' consent for this is obtained as part of the consent process.

Monitoring will be conducted as described in the SWIM Quality Management and Monitoring Plan: it is likely that each centre will be monitored by the sponsor or delegate at least once during the course of the trial, unless circumstances require that monitoring is done more frequently. At these visits, data stored on the database will be verified by comparison to source data.

### 10.3.2 Confidentiality

The patient's initials, gender, date of birth and hospital number will be collected and disclosed to the MRC CTU to enable database linkages. The participant's signed consent for this disclosure will be obtained.

Individual participants will not be identified in the resulting publications and presentations from the SWIM trial. SWIM will comply with the principles of the Data Protection Act.

### 10.3.3 Quality Assurance (QA) and Quality Control (QC) of Data

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled.

Copies of blood test results and drug charts will be requested.

# 11. SAFETY REPORTING

ICH GCP requires that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol. Section 11.1 lists definitions, section 11.2 gives details of the institution/investigator responsibilities and section 11.3 provides information on MRC CTU responsibilities.

## 11.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply in this trial protocol. These definitions are given in Table 3.

**Table 3: Definitions of Events**

| Term | Definition |
|---|---|
| **Adverse Event (AE)** | Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product. |
| **Adverse Reaction (AR)** | Any untoward and unintended response to an investigational medicinal product related to any dose administered. |
| **Unexpected Adverse Reaction (UAR)** | An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product. |
| **Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)** | Respectively any adverse event, adverse reaction or unexpected adverse reaction that:<br>□ results in death<br>□ is life-threatening*<br>□ requires hospitalisation or prolongation of existing hospitalisation**<br>□ results in persistent or significant disability or incapacity<br>□ consists of a congenital anomaly or birth defect<br>□ is another important medical condition*** |

**The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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, for example, a silent myocardial infarction.*

***Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.*

**** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AE or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.*

An investigational medicinal product is defined as the tested investigational medicinal product and the comparators used in the study. (EU guidance ENTR/CT 3, April 2006 revision)

## 11.2 Trial Specific Definitions

Adverse reactions include any untoward and unintended response to drugs

**Table 4: Adverse Events - Some inclusions and Exclusions**

| Adverse Events Include | Adverse Events Do Not Include |
|---|---|
| a) An exacerbation of a pre-existing illness<br><br>b) An increase in frequency or intensity of a pre-existing episodic event or condition<br><br>c) A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration<br><br>d) Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment | e) Medical or surgical procedures; the condition that leads to the procedure is the adverse event<br><br>f) Pre-existing disease or a condition present before treatment that does not worsen<br><br>g) Hospitalisations where no untoward or unintended response has occurred eg elective cosmetic surgery, social admissions<br><br>h) Overdose of medication without signs or symptoms |

## 11.3 Institution/Investigator Responsibilities

All non-serious AEs/ARs, whether expected or not, should be recorded in the 'sickle cell complications, side effects and additional treatment' section of the **SWIM Treatment Form** and sent to the MRC CTU within one month of the form being due. SAEs/SARs should be notified to the MRC CTU as described below.

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) in this trial should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) scale v 4.0: http://ctep.cancer.gov/reporting/ctc.html

A flowchart is given at the end of this section to help explain the notification procedures. Any questions concerning this process should be directed to the MRC CTU in the first instance.

### 11.3.1 Investigator Assessment

**(a) Seriousness**

When an AE/AR occurs the investigator responsible for the care of the patient must first assess whether the event is serious using the definition given in Table 3. If the event is serious and not exempt from expedited reporting, then an SAE form must be completed and the MRC CTU notified.

**(b) Causality**

The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions in Table 4. There are 5 categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related the event is classified as a SAE. If the causality is assessed as either possible, probable or definitely related then the event is classified as a SAR.

**Table 5: Definitions of Causality**

| Relationship | Description | Event Type |
|---|---|---|
| **Unrelated** | There is no evidence of any causal relationship | SAE |
| **Unlikely** | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment). | SAE |
| **Possible** | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments). | SAR |
| **Probable** | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. | SAR |
| **Definitely** | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. | SAR |

**(c) Expectedness**

If the event is a SAR the Investigator must assess the expectedness of the event. The definition of an unexpected adverse reaction (UAR) is given in Table 3. If a SAR is assessed as being unexpected it becomes a SUSAR.

**(d) Notification**

The MRC CTU should be notified within one working day of the investigator becoming aware of an event that requires expedited reporting. Investigators should notify the MRC CTU of all SAEs, SARs and SUSARS occurring from the time of randomisation until four weeks post-discharge.

**Notification Procedure:**

1. The SAE form must be completed by the Investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-fax to the MRC CTU as soon as possible. The initial report shall be followed by detailed, written reports as appropriate.

2. Send the SAE form by fax to the MRC CTU. Fax: 020 7670 4818

3. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form by ticking the box marked 'follow-up' and faxing to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be

identified by study number, date of birth and initials only. The patient's name should not be used on any correspondence.

4. Staff at the institution must notify their local research ethics committee (LREC) of the event (as per the institutions standard local procedure).

## 11.4 SWIM Notable Events

The following events are regarded as notable events in SWIM and should be notified to the MRC CTU within one working day using the Serious / Notable Adverse Event Reporting Form:

- Blood transfusion given
- Neurological symptoms
- Acute chest syndrome
- Any non-invasive respiratory support
- Transfers to Intensive Care

On the form, it should be specified whether an event is regarded as a SAE or a notable event.

## 11.5 Sponsor's Responsibilities

The Chief Investigator or other medically qualified delegates will review all SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.

## 11.6 MRC CTU's Responsibilities

The MRC CTU is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA) and the research ethics committees as appropriate.

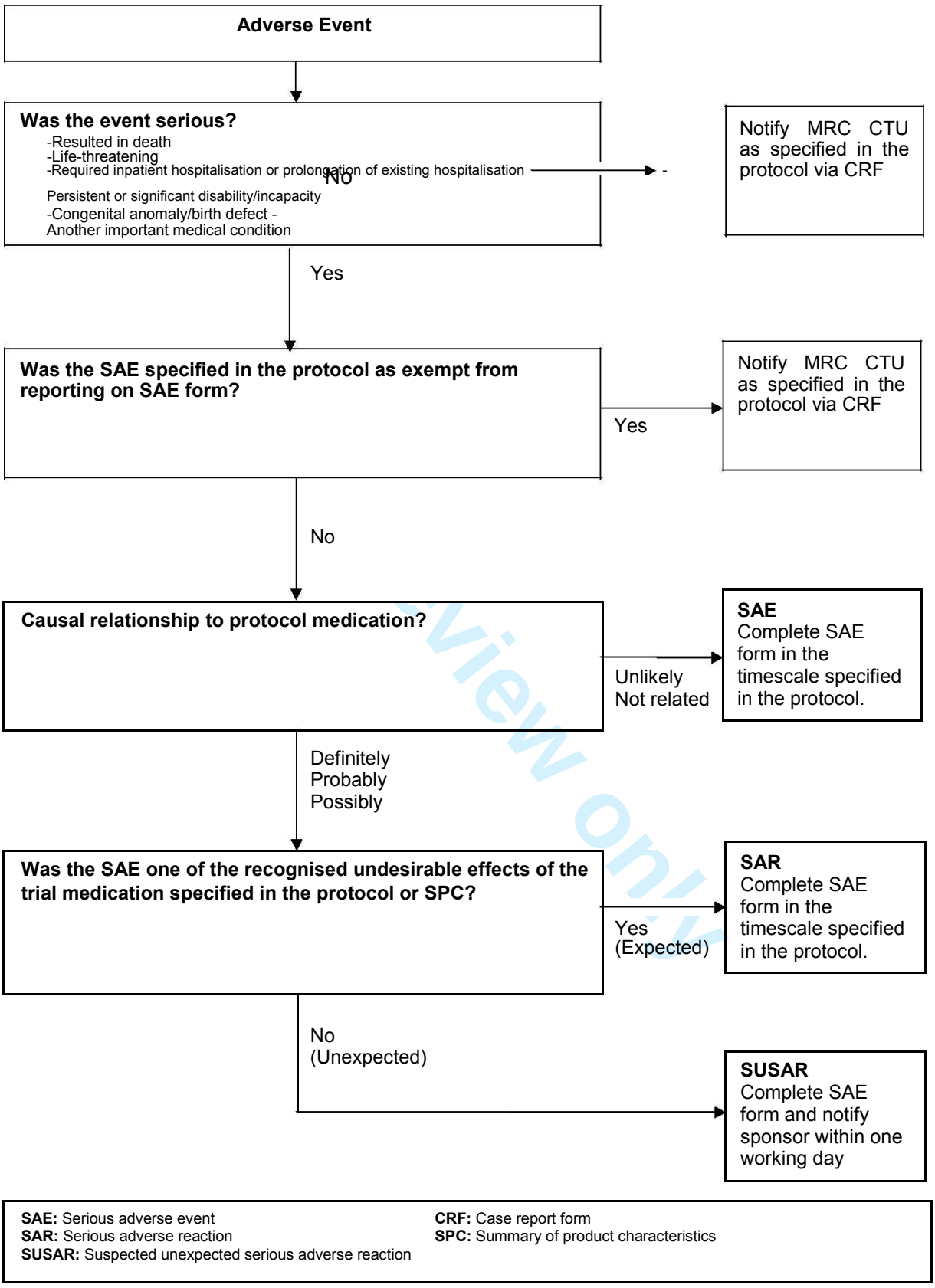
All investigators will be informed of any safety issues that arise during the course of the trial.

**SAE NOTIFICATION**

Within one working day of becoming aware of an SAE, please fax a completed SAE form to the MRC Clinical Trials Unit on:

**Fax: 020 7670 4818**

**Figure 2: Safety Reporting Flowchart**



# 12. ETHICAL CONSIDERATIONS AND APPROVAL

## 12.1 Ethical considerations

The study will abide by the principles of the Declaration of Helsinki version 2008.

Sickle cell disease is an inherited disorder of red blood cells and affects over 12,000 people in the UK of whom about 70% are in London. Better ways to manage sickle cell pain are required but hardly any research has been done in the UK to see how effective different painkillers are in the management of pain crisis in sickle cell disease.

This study has been developed with **input** from patients with sickle cell disease and the Sickle Cell Society. We hope to show that taking ibuprofen in addition to opioid through a PCA pump leads to substantial reduction in the use of opioid and related side effects for sickle cell pain treated in hospital. If this is the case, we anticipate that there would also be an overall improvement in patients' experience, and perhaps a reduction in NHS costs.

This study is a randomised controlled trial, and requires some patients to be given a **placebo** instead of ibruprofen in combination with opioid. This raises the main ethical issue, however the efficacy of this combination treatment has not been established and justifies the use of this 'gold standard' approach for a clinical trial.

**Consent** for participation of patients will be obtained twice:

- In the first instance, eligible patients will be approached in their regular outpatient clinic when they are pain free. Here they will be informed of the trial, given the Patient Information Sheet and provided with ample time and opportunity to discuss the trial with their Doctor and Research Nurse. If they agree to participate, they will be asked to sign the consent form and given a Patient Card to carry with them.
- In the second instance, consent will take the form of ‘verbal assent’ as in-patients when they are in pain and admitted to Accident and Emergency (A&E). They will be reminded of the trial and asked whether they still wish to participate in it. This process requires co−operation from A&E and Ward staff (doctors and nurses), therefore we plan to educate them about the study and train them to obtain verbal assent.

## 12.2 Ethical approval

The SWIM trial protocol v4.0, 7 October 2010 has received the favourable opinion of the London Research Ethics Committee but must undergo site specific assessment (SSA) by completing section C of the REC application form and submitting all sections of this form to the LREC. A copy of local R&D approval and of the PIS and CF on local headed paper should be forwarded to MRC CTU before patients are entered. Each patient’s consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient must remain free to

discontinue at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing his/her further treatment.

For details of any changes since the original version of the protocol that has been MREC-approved (v 0.2, 16 January 2009), see section 18.

# 13. REGULATORY ISSUES

The SWIM trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference number is 2008-006846-24.

## 13.1 Trial Closure

End of trial treatment will be at completion of the final patient's 4 week post-discharge clinic visit.

The trial will be considered closed 1 year after recruitment has been completed and data have been published.

# 14. INDEMNITY

The sponsor of the SWIM Study is the North West London Hospitals NHS Trust.

Below is a brief summary of the Indemnity arrangements in place on behalf of the sponsor:

**Negligent harm**
NHS Indemnity covers negligent harm(*) caused to patients or healthy volunteers in the following circumstances: whenever they are receiving an established treatment, whether or not in accordance with an agreed guideline or protocol; whenever they are receiving a novel or unusual treatment which, in the judgement of the health care professional, is appropriate for that particular patient; whenever they are subjects as patients or healthy volunteers of clinical research aimed at benefiting patients now or in the future.

(*) Clinical negligence is defined as “a breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process”.

**Non-negligent harm**
Apart from liability for defective products, legal liability does not arise where a person is harmed but no one has acted negligently. An example of this would be unexpected side-effects of drugs during clinical trials. In exceptional circumstances (and within the delegated limit of £50,000), NHS bodies may consider whether an ex-gratia payment could be offered. NHS bodies may not offer advance indemnities or take out commercial insurance for non-negligent harm.

# 15. FINANCE

The SWIM trial is being funded by the NIHR Health Technology Assessment Programme. The sponsor of the trial is the North West London Hospitals NHS Trust, and trial management will be coordinated at and by the MRC CTU in London.

# 16. TRIAL COMMITTEES

The SWIM trial will be co-ordinated at the MRC CTU in London. This trial is being undertaken in accordance with the Principles of GCP and in compliance with the Medicines for Human Use (Clinical Trials) regulations 2004. Collaborating investigators should be familiar with these guidelines, which are available from the MRC CTU or on the MRC website (http://www.mrc.ac.uk). Responsibilities of the trial personnel and committees are as follows:

## 16.1 Trial Management Team (TMT)

The MRC CTU TMT will include the Project Lead, Clinical Project Manager, Designated Statistician, Trial Manager and Data Manager and will meet at least monthly to discuss the general progress and day-to-day running of the trial. The TMT will monitor CRF return and data quality and deal with all aspects of the quality control procedures. Relevant issues will be referred to the TMG as required.

## 16.2 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and trial management representatives of the MRC Clinical Trials Unit. The TMG will oversee the day-to-day running and management of the trial and will provide progress reports to the Ethics Committee, MHRA and TSC. If there are specific safety concerns these may be raised with the TSC.

The TMG will initially (during the set up phase) meet monthly, and then at least 3 monthly. Meetings will be either face-to-face or via teleconference as needed.

Please refer to the SWIM TMG charter for more detail on its roles, functions and membership. All members of the TMG will be expected to sign the TMG charter.

## 16.3 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the trial and provide advice through an independent chairperson to the TMG on all aspects of the trial. The ultimate decision for the continuation of the trial lies with the TSC. TSC members will include persons independent of the trial investigators and the sponsor and will also include some members who are involved in the running the trial. The involvement of independent members who are not directly involved in other aspects of the trial provides protection for both trial participants and investigators. The TSC will select a chairperson (one of the independent members) during its first meeting. The TSC will meet at least annually either by teleconference or in person if needed.

Please refer to the SWIM TSC Charter for more detail on its roles, functions and membership. All members of the TSC will be expected to sign the TSC charter.

## 16.4 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be formed. The role of the IDMC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial. The IDMC will be the only group which sees the confidential, accumulating data by arm for the trial. The IDMC will see both safety and efficacy data for both treatment groups. Reports to the IDMC will be produced by the MRC CTU statisticians. The IDMC will meet within 6 months of the trial opening; the frequency of meetings will be specified in the IDMC charter. The IDMC will advise the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment be discontinued.

Please refer to the SWIM IDMC Charter for more detail on its roles, functions and membership. All members of the DMC will be expected to sign the DMC charter.

Further details of interim analysis and monitoring are provided in the IDMC charter and in section 9.4

# 17. PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications.

All publications shall include a list of participating centres, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN and EudraCT numbers associated with this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

No verbal or written report may be made without the approval of the TSC.

# 18. PROTOCOL AMENDMENTS

## 18.1 Version 2.0 (Dated 16 January 2009)

This version (v4.0, 7 October 2010) is the current version.

The first approved version of the protocol was v2.0, 16 January 2009. However, this version of the protocol was not circulated to participating centres and was superseded prior to the start of the trial.

The current version (v4.0, 7 October 2010) was substantially amended to bring the protocol in line with the MRC CTU's current preferred content format. .

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# APPENDIX 1: LOGS, CASE REPORT FORMS AND PATIENT-RELATED DOCUMENTS

**List of Logs:**

- Screening log
- Randomisation log

**List of CRFs:**

- Hospital anxiety and Depression Scale (HADS)
- Registration Form (form 1)
- Assessment of own health state Form. There are 9 different versions of this form corresponding to the stage of the trial at which they should be completed:
  - at consent (form 2)
  - on admission (form 4)
  - day 1 (form 7)
  - day 2 (form 9)
  - day 3 (form 11)
  - day 4 (form 13)
  - at discharge (form 16)
  - 1 week post-discharge (form 17)
  - 4 weeks post-discharge (form 18)
- Randomisation Form (form 3)
- Admission Details and Baseline Characteristics (form 5)
- SWIM Treatment Form. There are 4 versions of this form corresponding to the specific day of treatment:
  - Day 1 (form 6)
  - Day 2 (form 8)
  - Day 3 (form 10)
  - Day 4 (form 12)
- Daily Pain Scores Form (form 14)
- Discharge Form (form 15)
- SAE Form (form 19)

**List of patient-related documents:**

- Patient information sheet v4.0 (7 October 2010)
- Consent form v4.0 (7 October 2010)
- GP letter v4.0 (7 October 2010)

# APPENDIX 2: 5 STAGES OF CHRONIC KIDNEY DISEASE (CKD)

CKD is divided into 5 stages:-

1. CKD stage 1 is eGFR greater than 90 mls/min, with some sign of kidney damage on other tests (if all the other kidney tests are normal, there is no CKD).

2. CKD stage 2 is eGFR 60-90 with some sign of kidney damage (if all the kidney tests are normal, there is no CKD).

3. CKD stage 3 is eGFR 30-59 ml/min, a moderate reduction in kidney function

4. CKD stage 4 is eGFR 15-29 ml/min, a severe reduction in kidney function

5. CKD stage 5 is eGFR less than 15 ml/min, established kidney failure, when dialysis or a kidney transplant may be needed

http://www.kidney.org.uk/Medical-Info/ckd-info/

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | Title Page |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2-3 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4 |
| | 2b | Specific objectives or hypotheses | 4 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 4 |
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| Participants | 4a | Eligibility criteria for participants | 5 |
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| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 5 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 5 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | |
| Sample size | 7a | How sample size was determined | 5 |
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| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 5 |
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| | | | |
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| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | 11 |
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| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | |
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BMJ Open

# SWIM (Sickle With Ibuprofen and Morphine) Randomised Controlled Trial Fails To Recruit: Lessons Learned

| | |
|---|---|
| Journal: | *BMJ Open* |
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| Date Submitted by the Author: | 22-Mar-2016 |
| Complete List of Authors: | Cho, Gavin; London North West Healthcare NHS Trust, Central Middlesex Hospital, Haematology and Sickle Cell Centre<br>Anie, Kofi; London North West Healthcare NHS Trust, Central Middlesex Hospital, Haematology and Sickle Cell Centre; Imperial College Faculty of Medicine<br>Buckton, Jacky; London North West Healthcare NHS Trust, Central Middlesex Hospital, Haematology and Sickle Cell Centre<br>Kiilu, Patricia; London North West Healthcare NHS Trust, Central Middlesex Hospital, Haematology and Sickle Cell Centre<br>Layton, Mark; Imperial College, Department of Haematology<br>Alexander, Lydia; Imperial College Healthcare NHS Trust, Department of Haematology<br>Hemmaway, Claire; Barking Havering and Redbridge University Hospitals NHS Trust, Department of Haematology<br>Sutton, Dorothy; Barking Havering and Redbridge University Hospitals NHS Trust, Department of Haematology<br>Amos, Claire; MRC Clinical Trials Unit<br>Dore, Caroline; MRC Clinical Trials Unit<br>Kahan, Brennan; MRC Clinical Trials Unit,<br>Meredith, Sarah; MRC Clinical Trials Unit at UCL, |
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| Keywords: | PAIN MANAGEMENT, ACCIDENT & EMERGENCY MEDICINE, SICKLE CELL DISEASE, OPIOIDS, IBUPROFEN |
| | |

# SWIM (SICKLE WITH IBUPROFEN AND MORPHINE) RANDOMISED CONTROLLED TRIAL FAILS TO RECRUIT: LESSONS LEARNED

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ABSTRACT

**Objectives**

Sickle With Ibuprofen and Morphine (SWIM) Trial was designed to assess whether co-administration of ibuprofen (a non-steroidal anti-inflammatory drug) resulted in a reduction of opioid consumption delivered by patient controlled analgesia (PCA) for acute pain in sickle cell disease.

**Design**

A randomised, placebo-controlled, double-blind trial.

**Setting**

United Kingdom multicentre trial in acute hospital setting.

**Participants**

Adults with sickle cell disease of any gender and phenotype aged 16 years and over.

**Interventions**

Oral ibuprofen at a dose of 800mg three times daily or placebo in addition to opioids (morphine or diamorphine) administered via PCA pump for up to four days.

**Main outcome measures**

The primary outcome measure was opioid consumption over 4 days following randomisation.

**Results**

The SWIM trial closed early because it failed to randomise to its target of 316 patients within a reasonable time.

**Conclusions**

The key issues identified include the unanticipated length of time between informed consent and randomisation, difficulties in randomisation of patients in busy emergency departments, availability of trained staff at weekends and out of hours, fewer centres than expected using PCA routinely for sickle cell pain treatment, lack of research staff and support for participation, and the trial design. There are implications for future UK trials in sickle cell disease.

**Trial Registration**

ISRCTN Registry Identifier: ISRCTN97241637

ClinicalTrials.gov Identifier: NCT00880373

SUMMARY

**Strengths and limitations of this study**

- The SWIM trial was designed as a randomised, placebo controlled, double-blind trial.
- SWIM failed to achieve its target rate of patient randomisation.
- The implications for future UK sickle cell trials are discussed.

## BACKGROUND

Sickle cell disease comprises a group of genetic blood disorders that affect over 13,000 people in the UK predominantly of African, Caribbean, Asian, Arabian and Mediterranean origin. The hallmark symptom is pain. Over 50% of patients with sickle cell disease admitted to hospital in the UK have acute pain[1], commonly treated with opioids[2] with unpleasant side effects including nausea, constipation, itching, sedation and emotional changes.

Non-Steroidal Anti Inflammatory Drugs (NSAIDs) have been trialled in sickle cell disease, and are recommended[3]. However, a trial comparing ketoprofen with placebo plus syringe pump administered morphine in sickle cell disease failed to demonstrate a morphine sparing effect[4]. Ibuprofen analgesia is dose-related: a single 400mg dose offers one in three patients with moderate to severe pain at least 50% relief (number-needed-to-treat (NNT) of 2.7), compared with placebo; a single 600mg dose provides at least 50% pain relief to one in two patients (NNT of 1.7)[5]. Furthermore, patient controlled analgesia (PCA) using morphine in sickle cell disease provides adequate pain relief with reduced opioid consumption compared with continuous infusion[6].

## METHODS

'Sickle With Ibuprofen and Morphine' (SWIM) Trial, the first UK multicentre trial of analgesia in sickle cell disease, was a randomised, placebo controlled, double-blind trial of ibuprofen or placebo, to determine whether ibuprofen could reduce PCA opioid consumption for acute sickle cell pain.

The National Research Ethics Service, and Medicines and Healthcare products Regulatory Agency approved the SWIM trial.

**Participants and Recruitment**

Participants were adults (aged 16 years and over) with sickle cell disease of any phenotype, admitted to hospital with acute sickle cell pain for which opioids were warranted. Exclusions were: contraindications to morphine, diamorphine, or ibuprofen including peptic ulcers and NSAID induced asthma; renal dysfunction; stroke in preceding 6 weeks; pregnancy or breastfeeding.

Recruitment was in two stages:

1. Screening, informed consent and trial registration in outpatient clinics
2. Verbal assent and randomisation in Emergency Departments (A&E) on admission for sickle cell pain requiring opioid analgesia

Sample size calculation assumed a mean opioid consumption in the control group of 33mg (sd 43) over 4 days[6]. To detect a 50% reduction (90% power, 5% significance), required 286 patients; the recruitment target of 316 (158 per arm) allowed for 10% attrition.

Patients were randomised (1:1) to oral ibuprofen 800mg three times daily, or matching placebo, in addition to morphine or diamorphine via PCA for a maximum of 4 days during hospitalisation. Randomisation used permuted blocks stratified by centre; each patient was randomised only once by assigning the patient to the next available treatment pack number with the allocation sequence generated by the MRC Clinical Trials Unit.

The primary outcome was opioid consumption over 4 days.

RESULTS

Daily pain and symptom scores were recorded over the 4 days (Table 1). Treatment effects and 95% confidence intervals were calculated using an unadjusted linear regression model.

The SWIM trial was terminated early by the NIHR HTA Programme due to the very slow randomisation rate. Patients were recruited over 16 months, 83 consented to the trial but only 7 patients were randomised (Figure 1). Two main issues emerged at closure. Firstly, although the number of consented patients increased steadily, there was often a long delay between consent and randomisation. Patients with sickle cell disease have unpredictable pain episodes, some of which may require A&E attendances and hospital admissions. Severely affected patients tend to be offered disease modifying treatment such as hydroxycarbamide or blood transfusions. During the trial period, most patients who had been consented did not have a sickle cell pain episode that required hospitalisation. One patient was admitted to another hospital which was not a trial centre at the time. Secondly, there was a low rate of participation by sickle cell disease treatment centres; 27 were approached, 5 did not respond, 12 declined, 10 expressed interest, 4 registered patients, and only 2 centres randomised patients (Table 2).

## DISCUSSION

Several contributory factors for early closure of the SWIM trial, and potential remedies were identified:

1. Monitoring of emergency admissions for sickle cell pain at the lead trial centre found that 11 registered patients were not randomised because they presented at A&E during weekends or at night when no SWIM trial trained staff were present. Good Clinical Practice (GCP) training of A&E staff performing randomisation was challenging due to high staff turnover. A SWIM trial specific GCP training package was developed, which was easier to deliver on a more frequent basis, but there was insufficient time for this to have an impact on randomisation rate.
2. A&E at the lead centre was closed overnight for a significant proportion of the study due to low staffing levels and safety concerns. Therefore, some registered patients were admitted to other centres. A system to allow randomisation of a registered patient

admitted at a different centre was planned which would have improved the randomisation rate.

3. A SWIM trial protocol amendment to allow randomisation for repeated admissions had been approved by the trial oversight committees but not implemented before closure[7].
4. The SWIM trial was adopted onto the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio. Nonetheless, initiation of trial centres was slow and research support was difficult to access. Several interested centres could not participate because they did not use opioid PCA. Other reasons included lack of research infrastructure, and anticipated difficulties with randomisation in busy A&Es.
5. Many recruited patients with sickle cell disease did not have frequent hospitalisations for pain episodes, with a longer than anticipated delay between consent and randomisation, although it was encouraging that only 25% of eligible patients declined to participate.

The SWIM trial was conducted within the UK National Health Service (NHS), and was unsuccessful due to lack of interest or capacity at several large sickle cell disease centres, overestimation of the number of eligible patients, and unanticipated delays between registration and randomisation. USA trials in sickle cell disease also failed to recruit[8-10]. Explanations cited include complex protocol design, insufficient staff, lack of research support, time constraints of clinical staff, requirement for trained staff at weekends and out of hours, involvement of multiple departments, and fewer than expected eligible or consenting patients. These reasons are similar to the SWIM trial, nonetheless specific strategies have to be adopted in the UK which has a different health service structure and no strong culture of sickle cell disease research to encourage successful participation Moreover, in a cohort of multicentre trials funded by either the UK Medical Research Council or Health Technology Assessment Programme (HTA), only 31% of the trials achieved their original recruitment target with 53% being awarded an extension, and this did not improve over time[11]. Some pre-identified trial centres did not participate as planned, and there were delays due to various reasons including issues with local research staff and clinical arrangements, logistics, and

regulatory approvals although cancer trials were more successful because of the previously established National Cancer Research Network[11]. Therefore, it appears that specialty clinical research networks such as those 30 prioritised by the National Institute of Health Research (NIHR) for clinical research networks subsequent to the earlier ones in the areas of medicines for children, stroke, diabetes, and Alzheimer's disease would enhance recruitment.

There is a clinical need for research to improve treatment and outcomes in sickle cell disease within the NHS. The NIHR CRN portfolio provides funding, however this is based on patients randomised, rather than patients consented and recruited. In addition, CRN research capacity funds are usually awarded competitively based on research activity. Therefore, research inactive sickle cell disease centres are unlikely to be awarded funds for staff or capacity building to enable participation in trials such as SWIM. A case could be made for research in sickle cell disease to be affiliated to a specialty network to overcome these barriers.

Many HTA funded trials incorporate a feasibility phase. The SWIM trial was in response to a priority commissioned funding opportunity, and no preliminary work had been done to identify potential problems in recruitment. Six monthly progress reports highlighted recruitment problems. Plans to address these included an amendment of the original trial design to allow each patient to be randomised on more than one occasion, as opposed to participating only once. This could have increased the accrual rate during the first year by an additional 13 randomisations. An extension of the trial was proposed to the HTA Board, however this would have required additional funding, hence closure was not avoided.

These issues need to be addressed otherwise sickle cell disease trials in the UK will continue to fail.

## DATA SHARING

No additional data available.

## ACKNOWLEDGEMENTS

The trial was funded by the HTA Programme of the NIHR in the UK (Grant No. 07/48/01), and sponsored by London North West Healthcare NHS Trust.

We are extremely grateful to all the participants of the SWIM trial. We express our sincere gratitude to the R&D Department of the London North West Healthcare NHS Trust, and in particular Dr Alan Warnes and Simon Lewis for their relentless effort and extensive support. The contents of this manuscript are solely the responsibility of the authors and do not represent the views of the HTA Programme, NIHR, or London North West Healthcare NHS Trust.

## AUTHORS CONTRIBUTION

The SWIM trial was a collaborative effort between NHS Trusts and the MRC Clinical Trials Unit. Gavin Cho was the chief investigator; Kofi Anie, Mark Layton, and Claire Hemmaway were co-principal investigators; Jacky Buckton was the trial coordinator; Patricia Kiilu, Lydia Alexander, and Dorothy Sutton were involved in patient recruitment. Claire Amos was the MRC Clinical Trials Unit project manager; Caroline Doré and Brennan Kahan were trial statisticians; Sarah Meredith was the head of clinical operations. Kofi Anie took the lead in the write up with contributions, review and editing by the other authors.

## COMPETING INTERESTS

The authors have no competing interests.

The corresponding author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that there are not any discrepancies from the study as planned.

LICENCE AGREEMENT

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**Table 1: Clinical outcomes for each treatment arm**

| | Ibuprofen (n=2) | Placebo (n=5) | Difference in means (Ibuprofen vs. placebo) (95% CI) |
|---|---|---|---|
| Opioid consumption over 4 days (mg) – mean (SD) | 110 (45) | 206 (104) | -96 (-301 to 109) |
| Pain score over 4 days* – mean (SD) | 1.5 (0.7) | 3.2 (1.4) | -1.7 (-4.4 to 1.1) |
| Number of self-reported side effects per patient** (mild , moderate, or severe) – mean (SD) | 7.5 (0.7) | 10.2 (2.2) | -2.7 (-6.9 to 1.5) |
| Number of self-reported side effects per patient** (severe) – mean (SD) | 3.0 (1.4) | 3.2 (3.1) | -0.2 (-6.3 to 5.9) |

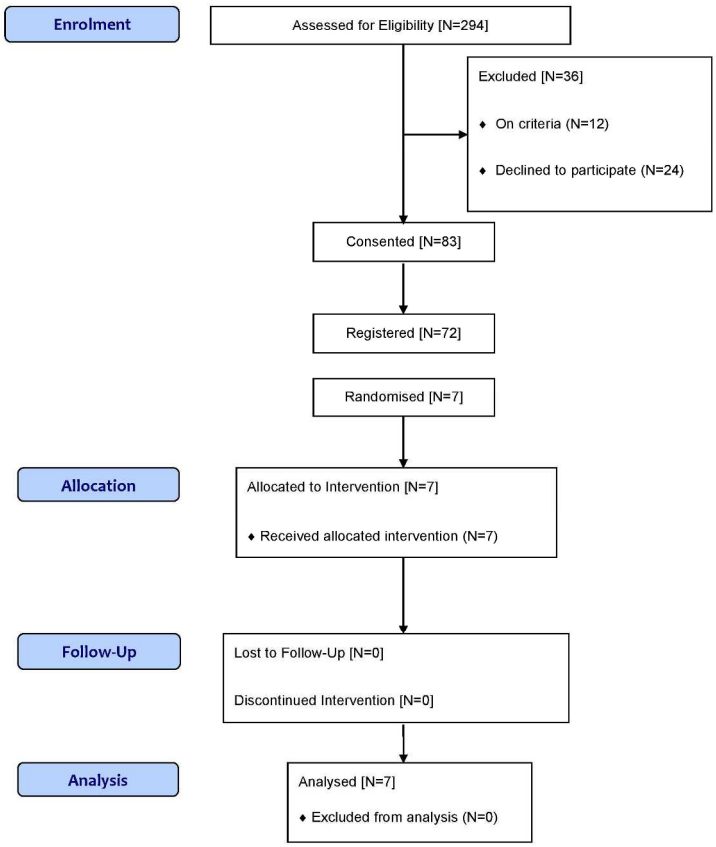
*Pain scores were measured using a 10 point scale (0 to 10) with higher scores indicating more pain.

**Self-reported side effects included nausea, vomiting, diarrhoea, constipation, stomach pain/discomfort, blood in stool, mood/emotional changes, sleep disturbances, dizziness, headache, itching, dry mouth, sore chest, and breathing difficulties, and each symptom was graded as none, mild, moderate, or severe.

**Table 2: Status of Centre Enrolment at SWIM Trial Closure**

| Centre Status | Number |
|---|---|
| Recruitment commenced | 4 |
| Interested – ready to commence centre-specific approval | 2 |
| Interested – not ready to commence centre-specific approval | 4 |
| Declined – do not use PCA for sickle cell pain | 9 |
| Declined – staff issues, lack of research support, A&E recruitment issues | 3 |
| No response | 5 |
| Total | 27 |

**Figure 1: Patient recruitment at SWIM Trial Closure**




Flow Chart of Patient Recruitment at SWIM Trial Closure
209x297mm (300 x 300 DPI)

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BMJ Open

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| Date Submitted by the Author: | 15-Apr-2016 |
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| Primary Subject Heading: | Haematology (incl blood transfusion) |
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| | |

# SWIM (SICKLE WITH IBUPROFEN AND MORPHINE) RANDOMISED CONTROLLED TRIAL FAILS TO RECRUIT: LESSONS LEARNED

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ABSTRACT

**Objectives**

Sickle With Ibuprofen and Morphine (SWIM) Trial was designed to assess whether co-administration of ibuprofen (a non-steroidal anti-inflammatory drug) resulted in a reduction of opioid consumption delivered by patient controlled analgesia (PCA) for acute pain in sickle cell disease.

**Design**

A randomised, placebo-controlled, double-blind trial.

**Setting**

United Kingdom multicentre trial in acute hospital setting.

**Participants**

Adults with sickle cell disease of any gender and phenotype aged 16 years and over.

**Interventions**

Oral ibuprofen at a dose of 800mg three times daily or placebo in addition to opioids (morphine or diamorphine) administered via PCA pump for up to four days.

**Main outcome measures**

The primary outcome measure was opioid consumption over 4 days following randomisation.

**Results**

The SWIM trial closed early because it failed to randomise to its target of 316 patients within a reasonable time.

**Conclusions**

The key issues identified include the unanticipated length of time between informed consent and randomisation, difficulties in randomisation of patients in busy emergency departments, availability of trained staff at weekends and out of hours, fewer centres than expected using PCA routinely for sickle cell pain treatment, lack of research staff and support for participation, and the trial design. There are implications for future UK trials in sickle cell disease.

**Trial Registration**

ISRCTN Registry Identifier: ISRCTN97241637

ClinicalTrials.gov Identifier: NCT00880373

SUMMARY

**Strengths and limitations of this study**

- The SWIM trial was designed as a randomised, placebo controlled, double-blind trial.
- SWIM failed to achieve its target rate of patient randomisation.
- The implications for future UK sickle cell trials are discussed.

## BACKGROUND

Sickle cell disease comprises a group of genetic blood disorders that affect over 13,000 people in the UK predominantly of African, Caribbean, Asian, Arabian and Mediterranean origin. The hallmark symptom is pain. Over 50% of patients with sickle cell disease admitted to hospital in the UK have acute pain[1], commonly treated with opioids[2] with unpleasant side effects including nausea, constipation, itching, sedation and emotional changes.

Non-Steroidal Anti Inflammatory Drugs (NSAIDs) have been trialled in sickle cell disease, and are recommended[3]. However, a trial comparing ketoprofen with placebo plus syringe pump administered morphine in sickle cell disease failed to demonstrate a morphine sparing effect[4]. Ibuprofen analgesia is dose-related: a single 400mg dose offers one in three patients with moderate to severe pain at least 50% relief (number-needed-to-treat (NNT) of 2.7), compared with placebo; a single 600mg dose provides at least 50% pain relief to one in two patients (NNT of 1.7)[5]. Furthermore, patient controlled analgesia (PCA) using morphine in sickle cell disease provides adequate pain relief with reduced opioid consumption compared with continuous infusion[6].

## METHODS

'Sickle With Ibuprofen and Morphine' (SWIM) Trial, the first UK multicentre trial of analgesia in sickle cell disease, was a randomised, placebo controlled, double-blind trial of ibuprofen or placebo, to determine whether ibuprofen could reduce PCA opioid consumption for acute sickle cell pain.

The National Research Ethics Service, and Medicines and Healthcare products Regulatory Agency approved the SWIM trial.

**Participants and Recruitment**

Participants were adults (aged 16 years and over) with sickle cell disease of any phenotype, admitted to hospital with acute sickle cell pain for which opioids were warranted. Exclusions were: contraindications to morphine, diamorphine, or ibuprofen including peptic ulcers and NSAID induced asthma; renal dysfunction; stroke in preceding 6 weeks; pregnancy or breastfeeding.

Recruitment was in two stages:

1. Screening, informed consent and trial registration in outpatient clinics
2. Verbal assent and randomisation in Emergency Departments (A&E) on admission for sickle cell pain requiring opioid analgesia

Sample size calculation assumed a mean opioid consumption in the control group of 33mg (sd 43) over 4 days[6]. To detect a 50% reduction (90% power, 5% significance), required 286 patients; the recruitment target of 316 (158 per arm) allowed for 10% attrition.

Patients were randomised (1:1) to oral ibuprofen 800mg three times daily, or matching placebo, in addition to morphine or diamorphine via PCA for a maximum of 4 days during hospitalisation. Randomisation used permuted blocks stratified by centre; each patient was randomised only once by assigning the patient to the next available treatment pack number with the allocation sequence generated by the MRC Clinical Trials Unit.

The primary outcome was opioid consumption over 4 days.

RESULTS

Daily pain and symptom scores were recorded over the 4 days (Table 1). Treatment effects and 95% confidence intervals were calculated using an unadjusted linear regression model.

The SWIM trial was terminated early by the NIHR HTA Programme due to the very slow randomisation rate. Patients were recruited over 16 months, 83 consented to the trial but only 7 patients were randomised (Figure 1). Two main issues emerged at closure. Firstly, although the number of patients giving their consent increased steadily, there was often a long delay between consent and randomisation. Patients with sickle cell disease have unpredictable pain episodes, some of which may require A&E attendances and hospital admissions. Severely affected patients tend to be offered disease-modifying treatment such as hydroxycarbamide (hydroxyurea) or blood transfusions. During the trial period, most patients who had given their consent did not have a sickle cell pain episode that required hospitalisation. One patient was admitted to another hospital which was not a trial centre at the time. Secondly, there was a low rate of participation by sickle cell disease treatment centres; 27 were approached, 5 did not respond, 12 declined, 10 expressed interest, 4 registered patients, and only 2 centres randomised patients (Table 2).

## DISCUSSION

Several contributory factors for early closure of the SWIM trial, and potential remedies were identified:

1. Monitoring of emergency admissions for sickle cell pain at the lead trial centre found that 11 registered patients were not randomised because they presented at A&E during weekends or at night when no SWIM trial trained staff were present. Good Clinical Practice (GCP) training of A&E staff performing randomisation was challenging due to high staff turnover. A SWIM trial specific GCP training package was developed, which was easier to deliver on a more frequent basis, but there was insufficient time for this to have an impact on randomisation rate.
2. A&E at the lead centre was closed overnight for a significant proportion of the study due to low staffing levels and safety concerns. Therefore, some registered patients were admitted to other centres. A system to allow randomisation of a registered patient

admitted at a different centre was planned which would have improved the randomisation rate.

3. A SWIM trial protocol amendment to allow randomisation for repeated admissions had been approved by the trial oversight committees but not implemented before closure[7].
4. The SWIM trial was adopted onto the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio. Nonetheless, initiation of trial centres was slow and research support was difficult to access. Several interested centres could not participate because they did not use opioid PCA. Other reasons included lack of research infrastructure, and anticipated difficulties with randomisation in busy A&Es.
5. Many recruited patients with sickle cell disease did not have frequent hospitalisations for pain episodes, with a longer than anticipated delay between consent and randomisation, although it was encouraging that only 25% of eligible patients declined to participate.

The SWIM trial was conducted within the UK National Health Service (NHS), and was unsuccessful due to lack of interest or capacity at several large sickle cell disease centres, overestimation of the number of eligible patients, and unanticipated delays between registration and randomisation. USA trials in sickle cell disease also failed to recruit[8-10]. Explanations cited include complex protocol design, insufficient staff, lack of research support, time constraints of clinical staff, requirement for trained staff at weekends and out of hours, involvement of multiple departments, and fewer than expected eligible or consenting patients. These reasons are similar to the SWIM trial, nonetheless specific strategies have to be adopted in the UK which has a different health service structure and no strong culture of sickle cell disease research to encourage successful participation Moreover, in a cohort of multicentre trials funded by either the UK Medical Research Council or Health Technology Assessment Programme (HTA), only 31% of the trials achieved their original recruitment target with 53% being awarded an extension, and this did not improve over time[11]. Some pre-identified trial centres did not participate as planned, and there were delays due to various reasons including issues with local research staff and clinical arrangements, logistics, and

regulatory approvals although cancer trials were more successful because of the previously established National Cancer Research Network[11]. Therefore, it appears that specialty clinical research networks such as those 30 prioritised by the National Institute of Health Research (NIHR) for clinical research networks subsequent to the earlier ones in the areas of medicines for children, stroke, diabetes, and Alzheimer's disease would enhance recruitment.

There is a clinical need for research to improve treatment and outcomes in sickle cell disease within the NHS. The NIHR CRN portfolio provides funding, however this is based on patients randomised, rather than patients giving consent and then recruited. In addition, CRN research capacity funds are usually awarded competitively based on research activity. Therefore, research inactive sickle cell disease centres are unlikely to be awarded funds for staff or capacity building to enable participation in trials such as SWIM. A case could be made for research in sickle cell disease to be affiliated to a specialty network to overcome these barriers.

Many HTA funded trials incorporate a feasibility phase. The SWIM trial was in response to a priority commissioned funding opportunity, and no preliminary work had been done to identify potential problems in recruitment. Six monthly progress reports highlighted recruitment problems. Plans to address these included an amendment of the original trial design to allow each patient to be randomised on more than one occasion, as opposed to participating only once. This could have increased the accrual rate during the first year by an additional 13 randomisations. An extension of the trial was proposed to the HTA Board, however this would have required additional funding, hence closure was not avoided.

These issues need to be addressed otherwise sickle cell disease trials in the UK will continue to fail.

## DATA SHARING

No additional data available.

## ACKNOWLEDGEMENTS

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## AUTHORS CONTRIBUTION

The SWIM trial was a collaborative effort between NHS Trusts and the MRC Clinical Trials Unit. Gavin Cho was the chief investigator; Kofi Anie, Mark Layton, and Claire Hemmaway were co-principal investigators; Jacky Buckton was the trial coordinator; Patricia Kiilu, Lydia Alexander, and Dorothy Sutton were involved in patient recruitment. Claire Amos was the MRC Clinical Trials Unit project manager; Caroline Doré and Brennan Kahan were trial statisticians; Sarah Meredith was the head of clinical operations. Kofi Anie took the lead in the write up with contributions, review and editing by the other authors.

## COMPETING INTERESTS

The authors have no competing interests.

The corresponding author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that there are not any discrepancies from the study as planned.

LICENCE AGREEMENT

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**Table 1: Clinical outcomes for each treatment arm**

| | Ibuprofen (n=2) | Placebo (n=5) | Difference in means (Ibuprofen vs. placebo) (95% CI) |
|---|---|---|---|
| Opioid consumption over 4 days (mg) – mean (SD) | 110 (45) | 206 (104) | -96 (-301 to 109) |
| Pain score over 4 days* – mean (SD) | 1.5 (0.7) | 3.2 (1.4) | -1.7 (-4.4 to 1.1) |
| Number of self-reported side effects per patient** (mild , moderate, or severe) – mean (SD) | 7.5 (0.7) | 10.2 (2.2) | -2.7 (-6.9 to 1.5) |
| Number of self-reported side effects per patient** (severe) – mean (SD) | 3.0 (1.4) | 3.2 (3.1) | -0.2 (-6.3 to 5.9) |

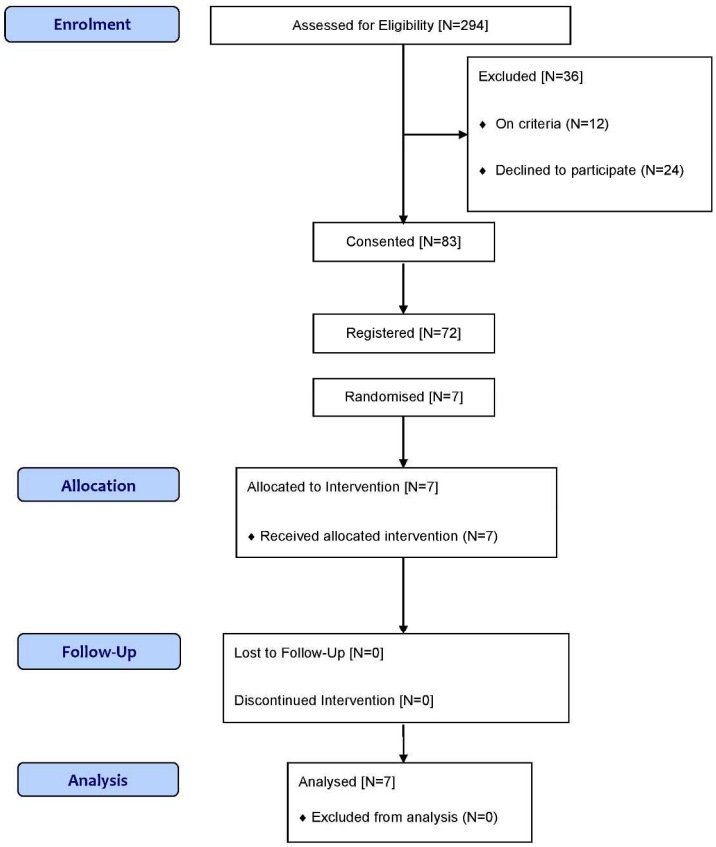
*Pain scores were measured using a 10 point scale (0 to 10) with higher scores indicating more pain.

**Self-reported side effects included nausea, vomiting, diarrhoea, constipation, stomach pain/discomfort, blood in stool, mood/emotional changes, sleep disturbances, dizziness, headache, itching, dry mouth, sore chest, and breathing difficulties, and each symptom was graded as none, mild, moderate, or severe.

**Table 2: Status of Centre Enrolment at SWIM Trial Closure**

| Centre Status | Number |
|---|---|
| Recruitment commenced | 4 |
| Interested – ready to commence centre-specific approval | 2 |
| Interested – not ready to commence centre-specific approval | 4 |
| Declined – do not use PCA for sickle cell pain | 9 |
| Declined – staff issues, lack of research support, A&E recruitment issues | 3 |
| No response | 5 |
| Total | 27 |

**Figure 1: Patient recruitment at SWIM Trial Closure**




Flow Chart of Patient Recruitment at SWIM Trial Closure
209x297mm (300 x 300 DPI)

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | Title Page |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2-3 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4 |
| | 2b | Specific objectives or hypotheses | 4 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 4 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | |
| Participants | 4a | Eligibility criteria for participants | 5 |
| | 4b | Settings and locations where the data were collected | 5 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 5 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 5 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | |
| Sample size | 7a | How sample size was determined | 5 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 5 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 5 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 5 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 5 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | 12 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | 12 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | 5 |
| | 14b | Why the trial ended or was stopped | 5 |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | 11 |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | 11 |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | 11 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 6-7 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 3 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 8 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.