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: UK 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 800 mg three times daily or placebo in addition to opioids (morphine or diamorphine) administered via PCA pump for up to 4 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 sickle cell disease trials.

Trial registration number: ISRCTN97241637, NCT00880373; Pre-results.

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,3 commonly treated with opioids2 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 400 mg 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 600 mg 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, designed to determine whether ibuprofen could reduce PCA opioid consumption for acute sickle cell pain.
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 33 mg (SD 43) over 4 days. 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 800 mg three times daily; or matching placebo, in addition to morphine or diamorphine via PCA for a maximum of 800 mg three times daily, or matching placebo, in addition of 316 (158 per arm) allowed for 10% attrition.

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% CIs 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. 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 (figure 1). Two main issues emerged at closure. First, 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. Second, 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:

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3. A SWIM trial protocol amendment to allow randomisation for repeated admissions had been approved

<table>
<thead>
<tr>
<th>Table 1 Clinical outcomes for each treatment arm</th>
<th>Ibuprofen (n=2)</th>
<th>Placebo (n=5)</th>
<th>Difference in means (Ibuprofen vs placebo) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid consumption over 4 days (mg)—mean (SD)</td>
<td>110 (45)</td>
<td>206 (104)</td>
<td>−96 (−301 to 109)</td>
</tr>
<tr>
<td>Pain score over 4 days*—mean (SD)</td>
<td>1.5 (0.7)</td>
<td>3.2 (1.4)</td>
<td>−1.7 (−4.4 to 1.1)</td>
</tr>
<tr>
<td>Number of self-reported side effects per patient† (mild, moderate, or severe)—mean (SD)</td>
<td>7.5 (0.7)</td>
<td>10.2 (2.2)</td>
<td>−2.7 (−6.9 to 1.5)</td>
</tr>
<tr>
<td>Number of self-reported side effects per patient† (severe)—mean (SD)</td>
<td>3.0 (1.4)</td>
<td>3.2 (3.1)</td>
<td>0.2 (−6.3 to 5.9)</td>
</tr>
</tbody>
</table>

*Pain scores were measured using a 10-point scale (0–10) 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.
by the trial oversight committees but not implemen-
ted before closure.7

4. The SWIM trial was adopted onto the National
Institute for Health Research Clinical Research
Network (NIHR CRN) portfolio. Nonetheless, initi-
ation 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 infra-
structure and anticipated difficulties with randomisa-
tion in busy A&Es.

5. Many recruited patients with sickle cell disease did
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 eli-
gible patients, and unanticipated delays between registra-
tion 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, spe-
cific 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 preidentified trial

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**Figure 1** Flow chart of patient recruitment at SWIM trial closure.
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. 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.

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**Acknowledgements** The trial was funded by the HTA Programme of the NIHR in the UK (grant number 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.

**Contributors** The SWIM trial was a collaborative effort between NHS Trusts and the MRC Clinical Trials Unit. GC was the chief investigator; KAA, ML, and OH were co-principal investigators; JB was the trial coordinator; PK, LA, and DS were involved in patient recruitment. CA was the MRC Clinical Trials Unit project manager; CJD and BK were trial statisticians; SM was the head of clinical operations. KAA took the lead in the write up with contributions, review and editing by the other authors.

**Funding** Health Technology Assessment Programme (grant number 07/48/01).

**Competing interests** None declared.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

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