Study summary

A comparison of Mirena use in Women with and without Fibroids

(short title: Mirena and Fibroids)
Eudract number: 2011-001461-40
REC ref: Yorkshire and the Humber REC
11/NE/0311
(previously East Yorkshire and Lincolnshire REC 11/YH/0021)
(originally Hull and East Riding REC 07/H1304/97)
Sponsor ref: Hull and East Yorkshire NHS Trust
R1159
(previously R0596)
UKCRN number: Y CSP 74414

Summary in brief

This study was originally conceived in March 2007 in order to investigate the clinical controversy of the use of the levonorgestrel-releasing intrauterine system (Mirena) in women with uterine fibroids. Multiple problems were encountered with changes in clinical research governance arrangements, changes in research personnel and changes in clinical care provision within the NHS. Eventually the study was stopped in May 2012 after only two subjects had been recruited. No scientific conclusions were possible.

This summary will consist of the following -

1. A restating of the scientific background of the study
2. A copy of the final protocol
3. Details of the problems encountered in chronological order

1. Scientific justification of the Study

Fibroids are the commonest human tumour with an incidence of up to 70% of premenopausal women.[1] Their most common presentation is heavy periods and they probably account for 30,000 hysterectomies in the UK every year.[2] The most recent NICE guideline on the treatment of heavy periods considers hysterectomy to be performed too readily and advocates the use of Mirena as the treatment of first choice for all patients with heavy periods.[2]

Mirena is an intrauterine system designed for contraception and also licensed for the treatment of heavy periods.[3] It is currently also used in a number of postmenopausal hormone replacement regimens. The system has become particularly popular with both clinicians and users because of its low cost, ease of use, high efficacy and immediate reversibility. A number of descriptive studies[4-11] have demonstrated its usefulness in treating heavy periods in women with fibroid uteri and these are summarised in the table below.

However WHO guidelines[12] still advise against its contraceptive use in uteri with submucous fibroids. There appeared to be no experimental data to support this

statement and despite the NICE recommendation no controlled studies had been performed comparing Mirena in fibroid and non-fibroid uteri. One group claimed that their results for Mirena use in fibroid uteri were not as beneficial as had been shown previously with non-fibroid uteri, but their study was not comparative.[13] Case reports existed[14, 15] of fibroids reducing in size with Mirena use but no formal study had been performed.

There was hence a clear need for prospective comparative studies to determine in which cases of uterine fibroids Mirena was most and least useful.

Pictorial bloodloss assessment charts (PBAC),[16,17] rise in haemoglobin[18] and improvement in quality of life scores[19] were all well established ways of quantifying response to the treatment of menorrhagia.

Table listing the existing published evidence, at the time of the original protocol, for LNG-IUS use in women with uterine leiomyomas

	Study design and sample size	Study duration (months)	Results
Singer & Ikomi, 1994 [4]	Prospective pilot study of 5 women with menorrhagia	6–18	Reduction in MBL Treated with intrauterine progesterone device
Fong & Singh, 1999 [5]	Case report of a renal transplant patient with Menorrhagia	12	Reduction in MBL Increase in Hb
Starczewski & Iwanicki, 2000 [6]	Prospective non-comparative study of 12 women with severe menstrual bleeding fitted with the LNG-IUS	6–12	Reduction in MBL Normalization of Hb
Mercorio et al., 2003 [7]	Observational study of 19 women with recurrent Menorrhagia fitted with the LNG-IUS	12	Reduction in MBL Decrease in Hb 74% reported persistent Menorrhagia at the end of the study
Grigorieva et al., 2003 [8]	Prospective non-comparative study of 67 women with Uterine leiomyomas fitted with the LNG-IUS	12	Reduction in MBL Increase in Hb and ferritin 40% reported amenorrhoea at the end of the study
Rosa e Silva et al., 2005 [9]	Descriptive case series of 10 women with increased uterine bleeding fitted with the LNG-IUS	6	Reduction in MBL Normalization of Hb and haematocrit
Soysal & Soysal, 2005 [10]	Prospective, historically controlled study of 32 menorrhagic women fitted with the LNG- IUS and 32 treated with thermal balloon ablation	12	Similar reduction in MBL Similar increase in Hb
Sayed et al 2011[11]	Prospective randomized study of 58 women comparing LNG-IUS with combined oral contraceptive.		Treatment failed in 6 women using LNG-IUS and in 11 women using COC.

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2. The final protocol

The following is the final protocol in its entirity

Aims and objectives of the study
The overall aim of this study is to characterise how women with fibroid uteri respond to the use of Mirena in comparison to women with normal uteri, and hence to predict which patients will be most and least suited to its use, hence the following objectives.

1. To establish whether Mirena is as effective in reducing symptoms of menorrhagia in women with fibroids as in women with no fibroids
2. To establish whether Mirena has more side effects in women with fibroids than in women with no fibroids
3. To establish whether Mirena causes a reliable reduction in fibroid size or not
4. To establish whether side effects or effectiveness can be predicted by the type of uterine distortion caused by fibroids or where the Mirena is sited within the uterine cavity.

The study forms the experimental part of an MSc thesis to be submitted to Hull York Medical School in the summer of 2012 by Maria Crouch.

Design of study
A prospective observational comparative study

Methodology
Women who choose a Mirena as treatment for heavy periods may have the device inserted in a variety of clinics, situated in both primary and secondary care. As many clinics as possible will be identified and asked to pass on information sheets to their patients in order to allow them to volunteer for the study should they wish to do so.

All women complaining of menorrhagia who are about to be fitted, or who have just been fitted with a Mirena will be asked if they would agree to participate. They will be given an information leaflet about the study and invited to contact the lead researcher if they wish to volunteer. If the woman wishes to volunteer and subsequently contacts the lead researcher she will be asked to attend the IVF unit at the Women and Children's Hospital where she will sign initial consent and undergo a vaginal ultrasound scan. This first visit will be organised as soon as conveniently possible.

The ultrasound scan will record a 3D sweep in order to locate the presence of any fibroids and record their size and position, as well as the location of the Mirena. The patient's medical record will be consulted in order to establish the ease of Mirena insertion and the pre-insertion haemoglobin value. The pre-insertion bleeding pattern, dysmenorrhoea, heaviness of bleed and quality of life score will be determined using the pictorial blood loss assessment chart (PBAC) and the SF-36 QOL questionnaire.

These assessments will be completed at the initial scan and then at 3 and 6 months after Mirena insertion. Subjects will attend for a second ultrasound scan performed 6 months after Mirena insertion. The final contact with the patient will be at 12 months in order to establish if they are still using the Mirena. Contact at 3 and 12 months may be by phone or by post. The table below shows the timeline for the measured parameters and patient involvement.

	Recruitment	3 months	6 months	1 year
Attendance at Hospital	X		X	
Consent	X			
Ultrasound scan	X		X	
PBAC	X	X	X	
Hb estimation	X		X	
QoL questionnaire	X	X	X	
Contact by Researcher	X	X	X	X

Inclusion criteria

All women who choose to have a Mirena IUS fitted as treatment for menorrhagia in one of the participating clinics.

Statistical analysis and power calculation

Our aim is to recruit 200 patients. In a group of this size with menorrhagia at least 100 would be expected to have fibroids. This should allow for dropouts and for the following calculations.

(1) Menstrual bloodloss. The primary comparison will be between fibroid and non-fibroid uteri with regard to reduction in menstrual blood loss (MBL). MBL is known to be log normally distributed throughout the population with some 11% loosing more than 80mls per month[15] and therefore classed as having objective menorrhagia. In menorrhagic women without fibroids Mirena insertion leads to a reduction in blood loss of the order of 80% by the third month of treatment.[21,22] A reduction of only 50% (that is 37% less) would be clinically significant and have value in terms of advice about who should use Mirena.

In the original study of Mirena use in women with menorrhagia but without fibroids[22] baseline menstrual blood loss was 176 (80-381) mls and at 3 months this reduced to 24 (0-145) mls, which is a fall of 152 mls (86%). In women with fibroids we expect to see at least a 50% reduction (equivalent to a fall from baseline to 88 units). 100 patients in each group will have 95% power to detect a difference at 3 months (effect size of 0.78), with 5% significance. This is based on undertaking ANCOVA to take account of baseline values.

(2) Continuation rates. First year continuation rates are a crude but useful way of assessing overall usefulness of a device. They are an overall indicator of the side effects to efficacy ratio as assessed by the patient herself. A recently conducted audit of the local population recorded an 80% first year continuation rate for Mirena. If first year continuation rates were to be reduced from 80% to 40% by the presence of fibroids a sample size of 28 in each group would have 80% power, at the 5% level.

(3) Fibroid size. One study[8] that claimed a reduction in fibroid size by Mirena use recorded a reduction in mean volume from 30 (±29) mls to 19 (±21) mls. This gave a P value of <0.0001 in a group of 67 women. However this paper crucially excluded all women with uterine cavity distortion by fibroids. Fibroids that distort the uterine cavity should be even more susceptible to the progestogen secreted from Mirenas as they are much closer, and hence our group size of 100 should easily be able to confirm this finding (46 patients in each group would be required to detect a fall of 11 units, at 80% power and 5% significance).

The study will also compare difficulties with insertion and side effects (such as irregular bleeding pattern) and QoL scores.

The records show that over 800 Mirenas are inserted by the Hull and East Yorkshire NHS Hospitals Trust each year and therefore there should be no problem in attracting 100 subjects to each arm of the study within the time frame of the study (14 months Aug 2011 to Oct 2012).

Ethical concerns

The study will be performed subject to a Research Ethics Committee favourable opinion, Site Specific Assessment (SSA) approval, Hull and East Yorkshire Hospitals NHS Trust R&D approval and MHRA clinical trial authorisation (CTA).

Ethical approval will be sought from the national REC service for a single site research study. Hull and East Yorkshire Hospitals NHS Trust R&D department will be asked to be study sponsor.

Patients invited onto the trial will be given a full information leaflet and sign consent if they agree. Travel costs will be reimbursed up to a maximum of £50 per subject.

Storage of information

Study records will be kept on a password-protected laptop belonging to the University of Hull. Study numbers rather than names will be used. Contact details will be kept separately. The 3D ultrasound scanner, situated in the IVF unit, records images as a 3D sweep of the pelvis, which can be recorded so that they are identified by study number only. They can thus be linked to the study database but not to the named patient. Images and database can be stored for up to 15 years as per guidelines.

Personal details will need to be retained for the duration of the study in order to allow reimbursement of travel expenses and to allow contact from the lead researcher for the completion of QOL questionnaires. Personal details will not be retained at the end of the study.

Ultrasound recordings

Ultrasound scans will be performed on the IVF unit on a Monday evening or arrangements could be made for a Tuesday or Thursday according to patient preference. Symptoms with regard to efficacy and side effects can also be elicited

at this time. The lead researcher will book these scans with the unit and perform the scans herself although Prof Killick could perform some scans to increase the times available for convenience of the research subject. Scans will be performed vaginally and abdominally if necessary (i.e. if fibroids are large) so as to record a sweep or sweeps of each uterus to allow subsequent counting and measurements of fibroids and description of Mirena location.
Patients will be offered a female member of staff as a chaperone or they may bring a friend with them when they have their scans.

Funding
A request for funding has been made to the UK distributors of Mirena, Bayer Healthcare Ltd.

Adverse event reporting
Adverse events (AEs) will be reported in accordance with HEY R&D department's Safety Reporting standard operating procedure (R&D GCP SOP 07) to ensure compliance with UK Clinical Trial Regulations. Investigators will notify the sponsor (HEY R&D dept.) of serious adverse events **within 24hrs** of becoming aware of the event using the serious event initial and follow-up report forms provided by R&D. The sponsor, Hull and East Yorkshire Hospitals NHS Trust R&D department (HEY R&D dept.) will report fatal or life-threatening SUSARs to the MHRA within 7 days and follow-up information within a further 8 days. The sponsor will send all other SUSAR reports to the MHRA within a maximum of 15 days. The investigator will report fatal or life-threatening SUSARs to the Ethics Committee (EC) within 7 days and follow-up information within a further 8 days by following the request on the serious event initial and follow-up report forms. The investigator will send all other SUSAR reports to the EC within a maximum of 15 days.

All adverse events (serious and non-serious) will be recorded by the investigator in the patients' data collection folders (CRFs) using R&D's adverse event report form. All adverse events will be recorded by the investigator in the patients' medical records.

All AEs will be followed-up by the investigators until the event has resolved or a decision has been taken for no further follow-up.

<u>Pregnancy</u>
If a study patient falls pregnant whilst participating in the trial, the patient will be withdrawn. The patient will be followed up by visits or telephone contacts during pregnancy and at birth and at 3 months after the birth of the baby. Should there be a congenital anomaly or birth defect, then this will be reported as a SUSAR.

<u>Urgent safety measures (refer to R&D GCP SOP 09)</u>
The investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. These safety measures should be taken immediately and may be taken without prior authorization from the MHRA, REC or Trust.
However, the investigator must alert the sponsor (HEY R&D) as soon as possible of the urgent measures by contacting the R&D Office telephone number 461882

or 461903 (Mon – Fri 8am – 6pm) or the Trust Switchboard 875875 (out-of-office hours) and asking for either the R&D Director or the R&D Manager. The investigator or sponsor should phone the Clinical Trial Unit at the MHRA and discuss the issue with a medical advisor as soon as possible. Contact the MHRA CTU via the clinical trials for medicines helpline 020 7084 2456 (Monday - Friday 08:30 -16:30).

3. Timeline of study progress through clinical governance

This study originated in March 2007 and the first protocol received ethical approval in August 2007. Schering Healthcare Ltd agreed to provide funding for the study and a designated researcher started to undergo basic training for the ultrasound scanning required.

There seems to have been an initial communication problem with the NHS Trust R&D Dept who did not give official approval for the study to begin and also the researcher could not reach the required standard of ultrasound competency, so the study was delayed until a new researcher could be found.

A new researcher was found at the end of 2008 and reapplications made. Ethical and NHS Trust approval were eventually given for the new ultrasonically competent researcher in May 2009. This researcher was a junior doctor who was rotated to York Hospital. The assumption was made that the York NHS Trust would accept the paperwork from the Hull NHS Trust but this proved not to be the case and a long period of reapplication followed during which the researcher seriously injured his back and was unable to continue with the study. Once again the study was put on hold.

In December 2010 a new researcher was found and attempts made to recommence the study. By this time, however, the company distributing the Mirena in the UK had changed (from Schering Healthcare to Bayer) and research governance arrangements had become much more extensive. Originally the MRHA advice was that the study was not a CTIMP but subsequently reversed this decision, making a formal MRHA application necessary.

Bayer declined to continue with the offer of funding for the study based on the fact that some patients with submucous fibroids may have had a Mirena inserted outside the product license. The protocol could not be altered as all study interventions were after Mirena insertion.

The final version of the protocol received ethics approval in March 2011 and NHS Trust approval in August 2011.

In April 2011 the NHS Trust ceased to fund Mirena insertions. Previously over 800 had been inserted annually and hence the subject numbers available for recruitment were reduced dramatically. A poster was therefore prepared in order to advertise the study in as many peripheral clinics as possible and a request to use the poster submitted to the ethics committee. Following this

request it became apparent that the original ethics approval had been given by a committee that was not authorized to approve CTIMP studies. The study was therefore suspended for a third time, this time requiring extensive documentation to MHRA, REC and Trust sponsor while new complete approvals were prepared and submitted.

Ethics approval was obtained for the third time with yet another reference number in October 2011.

Two subjects were recruited onto the study and underwent their first scan and questionnaire completion in February 2012.

Methodological problems that became apparent with these two subjects include that the precision of uterine volume measurement using the current ultrasound technique is unlikely to enable a robust significant result with the numbers planned. The recruitment would need to be increased considerably or a technique found to measure fibroid volume more precisely, possibly magnetic resonance.

Sadly these delays led to the fact that the student researcher could not complete her MSc in her allotted time and she has had to reorganize the research component of her degree to another study.

Research governance timeline

Protocol version 1 dated	27.07.07
Application for R&D approval R0569	26.07.07
Ethics approval	21.08.07
Email from Sarah Cross of Schering stating protocol would be acceptable for commercial funding	20.12.07
Email from Yombo Graham anticipating methodological difficulties	01.01.08
Discussion with ultrasound tutors: researcher does not have requisite skills	Dec 2008
Email from ethics requiring annual update and details of new researcher	03.04.09
Email from R&D saying that approval had never been given (no communication after application 26.7.07) and that further documentation was required	16.04.09
Copy of email from Trust managers “looks fine to me”	08.05.09
Trust business unit approval	12.05.09
Ethics and R&D application for new researcher, Jo Freites, updating documents to version 3 with same protocol	18.05.09
R&D Trust approval	27.05.09
Request for annual update from NHS R&D	14.07.09
Realisation from R&D that approval had only just been given	14.07.09
Enquiry to Ethics to carry on study in York	27.10.09
York declines to accept previous paperwork and requires complete new application. Jo Freites unable to reply as he has seriously hurt his back.	Nov 2009
Letter to Ethics committee explaining that the study would need to be put on hold until another researcher found	01.12.09
Funding lost as Mirena distribution transferred from Schering to Bayer (original take over was 2006)	Feb 2010
University of Hull approached to ask for other sources of funding	11.05.10
Maria Crouch decided on project	09.12.10
REC informed that a new researcher found	20.01.11
Protocol discussed with Graeme Kerson of Bayer prior to funding application	20.01.11

Initial costings and protocol sent to Bayer	31.01.11
Statistical advice from Victoria Allgar	01.02.11
MRHA enquiry if approval necessary (verbally told not a CTIMP)	01.02.11
Maria accepted by HYMS for intercalated degree	02.02.11
REC application accepted	03.02.11
Application for consideration of adoption by UKCRN	08.02.11
Conditional approval from ethics committee	23.02.11
MHRA email saying that approval will be necessary for CTIMP	09.03.11
Final approval from ethics committee	28.03.11
Email from Bayer placing restrictions on funding	15.03.11
EudraCT number obtained	22.03.11
Technical problems with EudraCT submission: signatures	31.03.11
Funding confirmed by Bayer at national level	08.04.11
Funding decision reversed by international Bayer parent company	16.05.11
Technical problems with EudraCT submission: unreadable disc	23.05.11
UKCRN funding denied as commercial funding withdrawn	31.05.11
MHRA approval	08.06.11
NHS Trust approval	19.08.11
REC application for substantial amendment to include poster for recruitment submitted on CTIMP form	12.09.11
Informed that REC can only approve non-CTIMP studies and therefore study no longer approved	30.09.11
Study suspended while ethics problems sorted. Reapplications prepared and submitted to MHRA, REC, R&D	Oct 2011
REC approval with new reference	14.10.11
First (and only) two subjects attended for ultrasound scan	13.02.11
Trial finally discontinued	10.05.12

The final outcome is that two patients were recruited and brought through for questionnaire completion and their first ultrasound scan. The study cannot be completed because of the time available before the researcher needs to submit her MSc. The chief investigator and research supervisor will also retire at the end of the year. Both subjects have been informed. Their clinical care is unaltered. No information is available to address the initial aims of the study. It is the opinion of the chief investigator that this study has been destroyed by the bureaucratic governance process as detailed above.

Professor Stephen Killick