Reviewer's report

Title: A three-arm, multicenter, open-label randomized controlled trial of hydroxychloroquine and low-dose prednisone to treat recurrent pregnancy loss in women with undifferentiated connective tissue diseases: Protocol for the immunosuppressant regimens for Living Fetuses (ILIFE) Trial

Version: 0 Date: 11 Nov 2019

Reviewer: Jane Daniels

Reviewer's report:

Introduction
Would consider using the term recurrent miscarriage instead of recurrent spontaneous abortion throughout. The latter is preferred term in journals such as BJOG and AJOG, and by many women. Similarly, please don't refer to "RSA women" - describe the population as "women who have had recurrent miscarriages".

Please refer to systematic reviews eg Cochrane Database Syst Rev. 2014 Jul 4;(7); Medicine (Baltimore). 2015 Nov;94(45):e1732. ; RMD Open. 2019 Apr 28;5(1):e000924 or guidelines eg Hum Reprod Open. 2018 Apr 6;2018(2):hoy004. instead of individual trials, cite the treatment effect and grade of evidence and reflect on the anticipate treatment effect in women with UCTD compared to CTD or APS.

Methods
How are previous miscarriages verified- from reports from women or only those managed in a healthcare facility? Are there criteria around the gestational age/ trimester at which the miscarriage occurred?
The requirement for the presence of at least one autoantibody- is there a complete list of qualifying autoantibodies? Are there any thresholds for positivity or is the normal reference range for each hospital? If so, do these reference ranges apply to young women?
Can you be more specific regarding the maternal/ uterine exclusion criteria eg using Thessaloniki ESHRE/ESGE consensus criteria. Similarly, are all women with fibroids >5cm excluded, or only those with submucosal and/or intramural?
ALT/ AST - again, are the thresholds for normality centrally defined or according the laboratory/ analyser? Are the reference ranges tailored for women of reproductive age?
If you have to use sealed envelopes, can you include a method to verify that envelopes are used in order and not opened and resealed?
Are there any important prognostic variables you could use to stratify? With envelopes, it is probably only practical to stratify by one other variable, in addition to site.

How is the dose of HCQ determined?
Are the anticoagulants comparable in dose/ efficacy? Who makes the decision as to which one?
Is 24 weeks sufficiently long enough for pregnancy to occur? Other trials (eg ISRCTN92644181, ISRCTN15948785) use a window of 12 months.
Are women who are using assisted conception eligible?
Outcomes:
What assessments are taking place every 4 weeks? How do these relate to the outcome measures. Should the primary outcome be any live birth or term live birth?
Premature delivery should include all live births before 34 and 37 weeks.
Should you also include clinical pregnancy at 6-8 weeks and ongoing pregnancy at 12 weeks?
Clearer definitions are required for maternal infection, gestational diabetes, UCTD activity, progression to CTD.
I calculate the sample size for the main comparison to be 121 women per group.
Is the third group, HCQ and anticoagulant, are you recruiting the same number? You should adjust the sample size for multiple comparisons.
How confident are you that you will be able to obtain the primary outcome for all women? What proportion transfer between hospitals?
How confident are you that 85% of eligible women will get pregnant within 24 weeks. For comparable UK trials, in ISRCTN92644181 53% of screened women were randomised (32% did not get pregnant) and in ISRCTN15948785, 42% did not get pregnant.
The known and expected adverse events of each drug should be stated (perhaps in an appendix) and those that are pertinent to miscarriage should be explicitly collected.
Although all drugs and licenced and well used, but a process for identifying unexpected serious adverse drug reactions should be described.

Analysis:
You state the primary comparison is HCQ+prednisolone+anticoagulant versus anti-coagulant only.
Are the other potential comparisons planned (HCQ+anticoagulant vs anticoagulant only, HCQ+prednisolone+anticoagulant vs HCQ+anticoagulant). If yes, the level of significance should be adjusted for multiple comparisons eg Bonferroni adjustment.

How will the Data Monitoring and Safety Board review data but keep the investigators blind to the accruing comparison data? On what grounds will they initiate the Safety Management Team?

What is the incidence rate of UCTD in women of reproductive age in China? Can the number of potentially eligible women seen in the hospitals be estimated? What proportion of this estimate will need to be randomised in the trial recruitment period?

Level of interest
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published
Quality of figures
All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

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Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

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