PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Study Protocol of Financial Incentives for Smoking Cessation in Pregnancy (FISCP). A Randomised, Multicentre Study.
AUTHORS	Berlin, Noémi; Goldzahl, Leontine; Jusot, Florence; Berlin, Ivan

VERSION 1 - REVIEW

REVIEWER	Assoc Prof Marita Lynagh University of Newcastle Australia
REVIEW RETURNED	18-Mar-2016

GENERAL COMMENTS	Overall comment This protocol paper describes the design and methodology of a randomised controlled trial on the efficacy of financial incentives for encouraging abstinence in pregnant smokers. Smoking in pregnancy is a major public health issue and incentives have shown good potential for encouraging behaviour change more broadly, and in relation to smoking cessation. Compulsory revisions: Introduction Page 4, Line 50, The sentenced beginning, 'In 2010, 17.1% ….of pregnancy women…'. Remove the (N = ….) and round down the prevalence to 17%. In the same sentence, 'smoked in the last trimester' should be 'in their last trimester'. Page 4, line 55. Why is the number of births & source cited here in brackets? Use normal referencing format. Page 5, line 12, The authors describe the reduction in smoking by women in pregnancy and relapse post-delivery as 'anecdotal reports'. There is sufficient evidence across many countries to support these well established patterns and such evidence should be cited here. Page 5, line 19. The authors state that international data does not 'transpose' to the population of French pregnant smokers. Further explanation & justification would strengthen this argument. Page 5, Lines 23 – 54, the whole paragraph here on NRT seems unnecessary and does not add anything of value to the manuscript. If anything, it confuses the reader and detracts from the focus on incentives. Would suggest removing this section and mention of NRT in other places eg. Abstract, page 2, line 8.

	Page 6, line 10. The word 'the' is missing from the sentence 'The theoretical framework of … economics of smoking '. Page 6, lines 10 – 40. The focus of this whole paragraph is on taxation, or financial incentives as the 'stick' not the 'carrot', which contrasts with the aim of the study. I question the relevance and value of this discussion. There are other more relevant theoretical frameworks for incentives that should be discussed her eg. Contingency Management Theory and Bandura's well known work. Page 6, line 44. The research by Volpp and Cahill's meta-analysis addressing smoking cessation in the general population and are not specific to pregnancy. This distinction needs to be made clear. Page 10, line 4. The objective of the study as stated here & elsewhere in the manuscript, is to assess the efficacy of incentives on smoking abstinence. Do they authors view that 'smoking asbtinence' is different from 'smoking cessation'. Given that the study is recruiting 'smokers', isn't the first effect on cessation or quitting smoking and then maintained cessation or abstinence. Perhaps the authors may consider the addition of a second main outcome which is 'quitting' and the effectiveness of incentives on quit rate , together which the effect on maintained abstinence. Page 10, line 21. The word 'on' should be replaced with 'to' in the sentence "..selection bias from agreeing on being part of…" Methods Page 11, Line 25. Women who use 'tobacco products other than cigarettes' and 'e-cigarettes' are to be excluded from participation. What about women who use other substances eg. cannabis, methamphetamines etc… Data indicates that illicit drug users also tend to have high tobacco smoking rates, so excluding these women may be excluding an important potential high risk group who would still benefit from quitting smoking, even if they continue to use other substcances. Page 11, line 41. "the centre will randomise 15 women per year"?? Should this read "per month"? Page 12, line 54, there is a typing error at the words "in cas" Page 13, Line 12, the word "of" should be inserted into "do not allow buying tobacco" Page 15, line 5, there is a typing error "sudties" Page 16, line 39, A drop-out rate of 5% is used for estimating sample size requirements. Where did this estimate come from? It seems quite ambitious. Page 19, Both expired CO and Urinary cotinine are listed as biochemical measures of smoking status &/or abstinence. Why are both measures used? There is no justification of the reliability & validity of each of these biochemical measures. Data analysis Page 21, line 16, The sentence here beginning "The planned intervention…" is not grammatical correct & is confusing.

	Discussion Page 22, line 32, Same comment as above in regard to the sentence containing ”…birth outcomes much better the…”??

REVIEWER	Stephen T. Higgins University of Vermont USA
REVIEW RETURNED	19-Mar-2016

GENERAL COMMENTS	As the authors note, maternal smoking during pregnancy is among the leading causes of pregnancy complications and poor birth outcomes in developed countries. There is broad consensus regarding the need for improved smoking-cessation interventions for this vulnerable population and a financial incentives treatment model wherein pregnant women earn vouchers exchangeable for retail items contingent on biochemically confirmed abstinence from recent smoking is showing substantial promise for meeting this important need [1,2]. This report by Berlin and colleagues details a protocol for a single blind, randomized, two-parallel groups trial investigating this financial incentives model for smoking cessation among 398 pregnant and early postpartum women. Women will receive approximately 1 year of care---6 months antepartum & 6 months postpartum--depending on how far along the pregnancy is upon the woman's study entry. Sixteen maternity clinics located throughout France will participate, using midwives or physicians certified in smoking cessation to implement the interventions. All women will receive standard-of-care smoking-cessation support during pregnancy and a 20 € voucher redeemable for retail items for attending monthly scheduled clinic visits. Additionally, women assigned to the incentives condition will have the potential to earn a total of an additional 280 € in vouchers contingent on biochemically confirmed abstinence from cigarette smoking across those same monthly clinic visits (breath carbon monoxide level < 8 ppm) for total earnings of approximately 380 €. The schedule of potential incentive earnings is designed to support sustained abstinence by offering escalating voucher values for sustaining abstinence across consecutive clinic visits (40, 60, 80, 100), with a reset back contingency to initial lower value for resumption of smoking. Effects of the intervention on smoking abstinence, pregnancy outcomes, birth outcomes, and breastfeeding will be assessed, and cost-benefit analyses will be conducted. This is an important trial for many reasons, including being comprehensive in scope, building systematically on prior knowledge, and having the potential for substantial impact. In articulating the overarching rationale for the study, the investigators underscore determining whether this incentives intervention is efficacious in French smokers. That is certainly a sound rationale, especially from the practical perspective of the funding agency (France's National Cancer Institute). Important to keep in mind, however, is there is an abundance of evidence already supporting the efficacy of incentives with pregnant smokers in the U.S. and more recently in the U.K, along with emerging evidence on effectiveness and cost-effectiveness [1]. Results from a recent meta-analysis [2] on the efficacy of financial incentives for smoking cessation with pregnant women that included 8 controlled trials and 1,295 pregnant women, for example, indicated that women treated with incentives have 3.79

(2.74, 5.25) greater odds of antepartum abstinence and 3.60 (2.39, 5.43) greater odds at the longest follow-up assessment reported. There is no scientific reason that I am aware of to hypothesize a qualitatively different response among pregnant smokers in France, although parameters matter in incentives-based interventions [3] and the proposed trial will provide these investigators and French policy makers with important empirical information on how this particular variation of the incentives model performs in this new population and setting. As discussed more below, investigators often tweak the parameters of this general incentives model across trials and those changes certainly have the potential to change outcomes.

In my opinion, it is the multicenter feature of this trial that has the potential to make the most substantial scientific contribution to the development of this treatment model. The authors may want to underscore this more in the study rationale. The plan to conduct the trial across 16 maternity wards located in hospitals throughout France using clinical staff (mid wives and physicians) as interventionists is unprecedented in this literature. That feature has the characteristics of a Stage 3 effectiveness trial rather than a Stage 2 efficacy trial in treatment development parlance [4]. I am aware of only one prior Stage 3 effectiveness trial in this area [5], which was a successful and important single arm trial comparing cessation rates obtained with financial incentives to historical controls in a maternity ward of a large urban hospital, with implementation carried out by mid wives in coordination with the community tobacco interventionist. The proposed trial is obviously a larger effort by orders of magnitude in terms of number of hospitals involved, having them distributed throughout the country, and including a broad array of outcomes in addition to smoking cessation rates as well as a cost-benefit analysis. There has only been one formal cost-effectiveness study reported on this treatment model to date [6] and thus more information on that topic will be of considerable interest as well. Overall, these design features imbue the proposed trial with the potential for considerable impact in terms of the scientific development of this treatment model generally and for strategically positioning policy makers in France to be able to move forward expeditiously with implementation should the results warrant doing so.

With that potential for high impact in mind, I'd recommend that the protocol provide more details on (a) training plans for the interventionists, (b) monitoring fidelity to the incentives protocol, and (b) cost-benefit modeling. Those plans may very well be in place and omitted from the present report due to space constraints. If not, there are at least two prior successful multi-site effectiveness trials with incentives targeting illicit drug use disorders in non-pregnant populations [7,8], and a large training effort on the use of financial incentives as part of intensive outpatient treatment for illicit drug use disorders provided in the U.S. Veterans Hospital System [9]. It may be possible to get information on staff training, and sustaining treatment fidelity that was associated with these efforts by contacting the authors if that was something of interest. It merits underscoring that there is a large and strikingly positive literature on the use of financial incentives for reducing substance use in other populations that went largely went unmentioned in the present report but can be an important resource. The voucher-based financial incentives model for reducing substance use was first reported in 1991 as part of a multi-element outpatient treatment for cocaine dependence [10]. A programmatic series of literature reviews on that treatment

	approach with substance use disorders provide a continuous record from the seminal report through the present [11,12]. Between 1991 and 2015, 177 controlled studies have been published in peer-reviewed journals examining the efficacy of systematically delivered vouchers or related monetary incentives for reducing drug use (vast majority of studies) or increasing adherence with other treatment regimens such as clinic attendance or medication adherence. Results in 88% (156/177) of those studies have demonstrated efficacy. As one small but potentially relevant example of how that literature can be helpful to the present protocol is with regard to the structuring of incentive programs. The plan to provide a 20 € incentive to women in the intervention condition for adhering with the scheduled clinic visit and the remainder contingent on smoking status runs counter to common practice in that research literature where you put the entire incentive on both adhering to the scheduled visits and being biochemically confirmed abstinent. In terms of impacting drug use, providing incentives for attendance only is equivalent to providing no incentive at all4. If you design the incentive program for increasing abstinence effectively, you will get both--good attendance and abstinence. If you do as proposed, you run the risk of woman opting for the lower but also less effortful attendance incentive. At a minimum, you are lowering the overall magnitude of the incentive contingent on abstinence, which in meta-analysis decreases treatment effect size4. If assessing all study participants at common time points is the goal, then convention is to schedule separate assessment sessions for all participants where compensation is provided for completing the assessment independent of drug use status. Put briefly, the size of the treatment effect of their intervention on smoking status in the proposed trial could likely be increased by combining the approximately 100 € in incentives that in the current plan will be provided for attendance with the approximately 280 € available for smoking abstinence and make the entire sum available for adhering with both the scheduled visit and being abstinent from smoking. I have no further comments and commend Berlin and colleagues on an outstanding and potentially high impact protocol and report. References 1. Higgins ST, Solomon LJ. Some recent developments on financial incentives for smoking cessation among pregnant and newly postpartum women. Curr Addict Rep. 2016; 3 (1): 9-18. 2. Cahill K, Hartmann-Boyce J, Perera R. Incentives for smoking cessation. Cochrane Database Syst Rev. 2015; May 18;5CD004307. [PubMed: 25983287] 3. Lussier JP, Heil SH, Mongeon JA. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. Addiction. 2006; 101(2): 192-203. [PubMed: 16445548] 4. Rounsaville BJ, Carroll KM, Onken LS. A stage model of behavioral therapies research: getting started and moving on from Stage I. Clin Psychol Sci Pract. 2001; 8:133–142. 5. Ierfino D, Mantzari E, Hirst J, Jones T, Aveyard P, Marteau T. Financial incentives for smoking cessation in pregnancy: a single-arm intervention study assessing cessation and gaming. Addiction. 2015; 110:680–8. [PubMed: 25727238]

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12. Davis DR.; Kurti AN.; Redner R.; et al. A Review of the literature on contingency management in the treatment of substance use disorders, 2009-2015. Poster presented at the 3rd annual conference on Behavior Change, Health, and Health Disparities, Oct 2-3, 2015, Burlington, VT.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Assoc Prof Marita Lynagh
Institution and Country
University of Newcastle
Australia
Please state any competing interests or state 'None declared':
None declared

Thank you for having reviewed this manuscript.
Overall comment
This protocol paper describes the design and methodology of a randomised controlled trial on the efficacy of financial incentives for encouraging abstinence in pregnant smokers. Smoking in pregnancy is a major public health issue and incentives have shown good potential for encouraging behaviour change more broadly, and in relation to smoking cessation.
Compulsory revisions:

Introduction
Page 4, Line 50, The sentenced beginning, ‘In 2010, 17.1% ….of pregnancy women…’. Remove the (N = ….) and round down the prevalence to 17%. In the same sentence, ‘smoked in the last trimester’ should be ‘in their last trimester’.
Response: Although we think that it is always useful to provide the exact N of a sample, we made the suggested modification.
Page 4, line 55. Why is the number of births & source cited here in brackets? Use normal referencing format.
Response: Done.

Page 5, line 12, The authors describe the reduction in smoking by women in pregnancy and relapse post-delivery as ‘anecdotal reports’. There is sufficient evidence across many countries to support these well established patterns and such evidence should be cited here.
Response: Post-partum relapse rate varies according the country of origin. From France, we are aware of only one paper about post-partum relapse rate; it is from 2001 and the sample size is relatively low (Lelong N, Kaminski M, Saurel-Cubizolles MJ, Bouvier-Colle MH.Postpartum return to smoking among usual smokers who quit during pregnancy. Eur J Public Health. 2001 Sep;11(3):334-9.) We modified the sentence and added some international references.

Page 5, line 19. The authors state that international data does not ‘transpose’ to the population of French pregnant smokers. Further explanation & justification would strengthen this argument.
Response: Unfortunately, it is frequent to transpose automatically data collected in one country or in one continent to other countries or continents. Biological (phenotype) and in particular behavioral data are influenced by cultural, socioeconomic and even by genetic factors so any transposition, not taking into account a country’s or region’s specific characteristics may be more or less biased. We completed this paragraph (page 5, 1st paragraph).
Page 5, Lines 23 – 54, the whole paragraph here on NRT seems unnecessary and does not add anything of value to the manuscript. If anything, it confuses the reader and detracts from the focus on incentives. Would suggest removing this section and mention of NRT in other places eg. Abstract, page 2, line 8.
Response: We think that a detailed paragraph about NRT in pregnancy is important because it is a main justification for looking for other interventions; this is warranted in particular in a study protocol aiming to assess another intervention, in this case, financial incentives. The Abstract mentions in one sentence NRT. We are afraid that one cannot lengthen the Abstract.
Page 6, line 10. The word ‘the’ is missing from the sentence ‘The theoretical framework of … economics of smoking ‘.
Response: Corrected.
Page 6, lines 10 – 40. The focus of this whole paragraph is on taxation, or financial incentives as the ‘stick’ not the ‘carrot’, which contrasts with the aim of the study. I question the relevance and value of this discussion. There are other more relevant theoretical frameworks for incentives that should be discussed her eg. Contingency Management Theory and Bandura’s well known work.
Response: As it is a joint medical and economics study protocol, we believe it is quite important to mention other economic (as opposed to medical) instruments that have been implemented to reduce tobacco consumption, even on the supply side, as it is the case of taxation. Not mentioning the existence of taxation as a financial incentive against tobacco consumption might be misleading.
The effect of financial incentives, as part of contingency management, on smoking cessation are discussed among the existing trials further down.
We mention the meta-analysis of self-efficacy and smoking (Gwalteney et al 2009) on page 8, paragraph 3. We agree that self-efficacy, as stated in Bandura’s theory, can be reinforced by financial incentives. A high level of self-efficacy could be assumed to help smokers to quit smoking, and that incentives would be a way to reinforce self-efficacy. However, in our study, we do not specifically make assumptions on the effect of self-efficacy level on the ability to succeed in smoking cessation.

When analyzing the results, discussion could be made on the interaction between self-efficacy and financial incentives (we do have a measure of locus of control that can be used as a proxy of self-efficacy). At the stage of the protocol it seems too hypothetical to mention Bandura's theories that could have an effect on smoking abstinence.
Page 6, line 44. The research by Volpp and Cahill's meta-analysis addressing smoking cessation in the general population and are not specific to pregnancy. This distinction needs to be made clear.
Response: We rewrote this paragraph mentioning now the results of the Cahill et al. 2015, the updated Cochrane review about financial incentives and in particular, the sub-meta-analysis of pregnant smokers' studies (page 6, last paragraph).

Page 10, line 4. The objective of the study as stated here & elsewhere in the manuscript, is to assess the efficacy of incentives on smoking abstinence. Do they authors view that 'smoking asbtinence' is different from 'smoking cessation'. Given that the study is recruiting 'smokers', isn't the first effect on cessation or quitting smoking and then maintained cessation or abstinence. Perhaps the authors may consider the addition of a second main outcome which is 'quitting' and the effectiveness of incentives on quit rate , together which the effect on maintained abstinence.
Response: We agree that cessation of smoking has two aspects: to trigger/induce cessation, an acute event, and to help maintain abstinence, a chronic event. Cessation is assessed post-quit by point prevalence abstinence rate. In practice, it seems very difficult to identify, in particular at the assessment level, the acute cessation because it can occur at any time. So because of the difficulty to specify acute cessation (what and when one can speak about cessation: one day after quit date? 1 week, 1 month etc after quit date?) we prefer not to change this paragraph. This is probably the reason why standard smoking cessation studies do not separate this two aspects of cessation i.e. quit and long-term (1 month end of treatment or more) abstinence rate.

Page 10, line 21. The word 'on' should be replaced with 'to' in the sentence "..selection bias from agreeing on being part of…"
Response: Correction done.

Methods
Page 11, Line 25. Women who use 'tobacco products other than cigarettes' and 'e-cigarettes' are to be excluded from participation. What about women who use other substances eg. cannabis, methamphetamines etc… Data indicates that illicit drug users also tend to have high tobacco smoking rates, so excluding these women may be excluding an important potential high risk group who would still benefit from quitting smoking, even if they continue to use other substcances.
Response: We agree that illicit drug users who are also smokers would benefit from quitting smoking. We therefore do not exclude illicit drug users. Therefore, this is not listed in this paragraph.

Page 11, line 41. "the centre will randomise 15 women per year"?? Should this read "per month"?
Response: No, the sentence is correct. 16 centres randomising 15 women per year= 240 women/year so in two years: 440 women. It would be a dream if our maternity wards would be able to randomize 15 women/month, that is 240 women per month.

Page 12, line 54, there is a typing error at the words "in cas"
Response: Correction done.

Page 13, Line 12, the word "of" should be inserted into "do not allow buying tobacco"
Response: Correction done.

Page 15, line 5, there is a typing error "sudties"
Response: Correction done.

Page 16, line 39, A drop-out rate of 5% is used for estimating sample size requirements. Where did this estimate come from? It seems quite ambitious.
Response: We agree that this is a relatively ambitious dropout rate. In Tappin et al. 2015, the lost to follow up rate is 14 % and 15 % at primary end point of gestational age of 34-38 weeks. But this study did not implement monthly, face-to-face visits. Because of the higher frequency of visits and because show-ups are rewarded by 20 euros, we estimate that our dropout rate will be better than that of Tappin et al. 2015. (See changes on page 16.)
Page 19, Both expired CO and Urinary cotinine are listed as biochemical measures of smoking status &/or abstinence. Why are both measures used? There is no justification of the reliability & validity of each of these biochemical measures.
Response: Abstinence in the study at visits is defined as self-report and expired air CO ≤ 8 ppm, an immediate result. However, we will do random urinary determinations to confirm smoking cessation (=no anabasine in urine) to control for gaming. Urinary cotinine will be used to check for NRT or tobacco use: e.g. cotinine + but anabasine – means NRT has been used but the woman is not smoking. See the detailed paragraph on page 18 on urine samples.

Data analysis
Page 21, line 16, The sentence here beginning “The planned intervention…” is not grammatical correct & is confusing.
Response: We rewrote this sentence.

Discussion
Page 22, line 32, Same comment as above in regard to the sentence containing ”…birth outcomes much better the…”??
Response: We rewrote this sentence.

Reviewer: 2
We thank the reviewer for having reviewed our manuscript.
Reviewer Name

Stephen T. Higgins

Institution and Country

University of Vermont
USA

Please state any competing interests or state ‘None declared’:

None declared.

Please leave your comments for the authors below
As the authors note, maternal smoking during pregnancy is among the leading causes of pregnancy complications and poor birth outcomes in developed countries. There is broad consensus regarding the need for improved smoking-cessation interventions for this vulnerable population and a financial incentives treatment model wherein pregnant women earn vouchers exchangeable for retail items contingent on biochemically confirmed abstinence from recent smoking is showing substantial promise for meeting this important need [1,2].

This report by Berlin and colleagues details a protocol for a single blind, randomized, two-parallel groups trial investigating this financial incentives model for smoking cessation among 398 pregnant

and early postpartum women. Women will receive approximately 1 year of care---6 months antepartum & 6 months postpartum--depending on how far along the pregnancy is upon the woman's study entry. Sixteen maternity clinics located throughout France will participate, using midwives or physicians certified in smoking cessation to implement the interventions. All women will receive standard-of-care smoking-cessation support during pregnancy and a 20 € voucher redeemable for retail items for attending monthly scheduled clinic visits. Additionally, women assigned to the incentives condition will have the potential to earn a total of an additional 280 € in vouchers contingent on biochemically confirmed abstinence from cigarette smoking across those same monthly clinic visits (breath carbon monoxide level < 8 ppm) for total earnings of approximately 380 €. The schedule of potential incentive earnings is designed to support sustained abstinence by offering escalating voucher values for sustaining abstinence across consecutive clinic visits (40, 60, 80, 100), with a reset back contingency to initial lower value for resumption of smoking. Effects of the intervention on smoking abstinence, pregnancy outcomes, birth outcomes, and breastfeeding will be assessed, and cost-benefit analyses will be conducted.

This is an important trial for many reasons, including being comprehensive in scope, building systematically on prior knowledge, and having the potential for substantial impact. In articulating the overarching rationale for the study, the investigators underscore determining whether this incentives intervention is efficacious in French smokers. That is certainly a sound rationale, especially from the practical perspective of the funding agency (France's National Cancer Institute). Important to keep in mind, however, is there is an abundance of evidence already supporting the efficacy of incentives with pregnant smokers in the U.S. and more recently in the U.K, along with emerging evidence on effectiveness and cost-effectiveness [1]. Results from a recent meta-analysis [2] on the efficacy of financial incentives for smoking cessation with pregnant women that included 8 controlled trials and 1,295 pregnant women, for example, indicated that women treated with incentives have 3.79 (2.74, 5.25) greater odds of antepartum abstinence and 3.60 (2.39, 5.43) greater odds at the longest follow-up assessment reported. There is no scientific reason that I am aware of to hypothesize a qualitatively different response among pregnant smokers in France, although parameters matter in incentives-based interventions [3] and the proposed trial will provide these investigators and French policy makers with important empirical information on how this particular variation of the incentives model performs in this new population and setting. As discussed more below, investigators often tweak the parameters of this general incentives model across trials and those changes certainly have the potential to change outcomes.

Response: Although we have now convincing meta-analyses about the efficacy of financial incentives to help pregnant smokers quit, at the time of the grant application in 2014, the results were more controversial (see the Cochrane review of Cahill and Perera of 2011). We agree that there is no major reason that financial incentives should not work similarly in France than in other countries. But to the best of our knowledge all data are from Anglo-Saxon countries with different cultural and health care system backgrounds compared to France. Thus, all treatments, especially the non-pharmacological ones that target behavioral modifications should be assessed in the specific target population. Moreover, probably no health care system would pay for financial incentives if their efficacy and cost-effectiveness are not demonstrated in the target population of the country that would pay for them. There is also the question of acceptability of this type of intervention by policy makers, by health care authorities but also by the general population that, at least in France, would pay by their mandatory health insurance contribution for the financial incentives if implemented.

In my opinion, it is the multicenter feature of this trial that has the potential to make the most substantial scientific contribution to the development of this treatment model. The authors may want to underscore this more in the study rationale. The plan to conduct the trial across 16 maternity wards located in hospitals throughout France using clinical staff (mid wives and physicians) as interventionists is unprecedented in this literature. That feature has the characteristics of a Stage 3 effectiveness trial rather than a Stage 2 efficacy trial in treatment development parlance [4]. I am aware of only one prior Stage 3 effectiveness trial in this area [5], which was a successful and

important single arm trial comparing cessation rates obtained with financial incentives to historical controls in a maternity ward of a large urban hospital, with implementation carried out by mid wives in coordination with the community tobacco interventionist. The proposed trial is obviously a larger effort by orders of magnitude in terms of number of hospitals involved, having them distributed throughout the country, and including a broad array of outcomes in addition to smoking cessation rates as well as a cost-benefit analysis. There has only been one formal cost-effectiveness study reported on this treatment model to date [6] and thus more information on that topic will be of considerable interest as well. Overall, these design features imbue the proposed trial with the potential for considerable impact in terms of the scientific development of this treatment model generally and for strategically positioning policy makers in France to be able to move forward expeditiously with implementation should the results warrant doing so.
Response: We agree that our trial is close to a Stage 3 effectiveness trial; it is, in fact, a mix between Stage 2 efficacy and Stage 3 effectiveness trial. We also hope to provide a straightforward cost-effectiveness analysis similar to that published by our colleagues from UK (Boyd et al. 2015).

With that potential for high impact in mind, I'd recommend that the protocol provide more details on (a) training plans for the interventionists, (b) monitoring fidelity to the incentives protocol, and (b) cost-benefit modeling. Those plans may very well be in place and omitted from the present report due to space constraints. If not, there are at least two prior successful multi-site effectiveness trials with incentives targeting illicit drug use disorders in non-pregnant populations [7,8], and a large training effort on the use of financial incentives as part of intensive outpatient treatment for illicit drug use disorders provided in the U.S. Veterans Hospital System [9]. It may be possible to get information on staff training, and sustaining treatment fidelity that was associated with these efforts by contacting the authors if that was something of interest. It merits underscoring that there is a large and strikingly positive literature on the use of financial incentives for reducing substance use in other populations that went largely went unmentioned in the present report but can be an important resource. The voucher-based financial incentives model for reducing substance use was first reported in 1991 as part of a multi-element outpatient treatment for cocaine dependence [10]. A programmatic series of literature reviews on that treatment approach with substance use disorders provide a continuous record from the seminal report through the present [11,12]. Between 1991 and 2015, 177 controlled studies have been published in peer-reviewed journals examining the efficacy of systematically delivered vouchers or related monetary incentives for reducing drug use (vast majority of studies) or increasing adherence with other treatment regimens such as clinic attendance or medication adherence. Results in 88% (156/177) of those studies have demonstrated efficacy. As one small but potentially relevant example of how that literature can be helpful to the present protocol is with regard to the structuring of incentive programs. The plan to provide a 20 € incentive to women in the intervention condition for adhering with the scheduled clinic visit and the remainder contingent on smoking status runs counter to common practice in that research literature where you put the entire incentive on both adhering to the scheduled visits and being biochemically confirmed abstinent. In terms of impacting drug use, providing incentives for attendance only is equivalent to providing no incentive at all4. If you design the incentive program for increasing abstinence effectively, you will get both--good attendance and abstinence. If you do as proposed, you run the risk of woman opting for the lower but also less effortful attendance incentive. At a minimum, you are lowering the overall magnitude of the incentive contingent on abstinence, which in meta-analysis decreases treatment effect size4. If assessing all study participants at common time points is the goal, then convention is to schedule separate assessment sessions for all participants where compensation is provided for completing the assessment independent of drug use status. Put briefly, the size of the treatment effect of their intervention on smoking status in the proposed trial could likely be increased by combining the approximately 100 € in incentives that in the current plan will be provided for attendance with the approximately 280 € available for smoking abstinence and make the entire sum available for adhering with both the scheduled visit and being abstinent from smoking.
Response:

Training plans for the interventionists: As mentioned in the manuscript/research protocol all investigators had previously been trained for smoking cessation in pregnancy (post-graduate training course of at least 80 hours, exam, diploma) and all routinely manage pregnant smokers. We already had a pre-study investigators' meeting specifying treatment goals and trying to uniformize the ways to obtain them. A second investigators meeting whose agenda includes revision of investigators' interaction with participants is planned for June 2016.
Monitoring fidelity to the incentives protocol: We evidently will monitor handling of vouchers up to giving them to participants but no dispositions are planned for checking of their use by participants.
The cost-benefit analysis: As in Boyd et al. (2015), we will produce a within-trial analysis and a life-time analysis. The effectiveness in the within-trial analysis will be as assessed according to the main outcome measure adjusted for the urinary anabasine validated smoking abstinence rate.
The direct health-care costs for each arm of the trial will be compared: costs of cessation support consultations with mid-wives, eventual NRT costs and costs of financial incentives: number of visits, show-up costs and effective financial incentives in the intervention group. We will add a benchmark scenario: usual cessation support without any financial incentives (neither for attendance nor for abstinence).
The life-time analysis will capture any short or long term health benefits of quitting smoking in QALYS and costs to health services. A Markov model will be used to consider any possible outcomes (relapse, quitting, tobacco and non tobacco related health disorders or death in a lifetime.
The model will be run for the control and for the financial incentive group in order to calculate the cost and QALYs for each group. We will also run the model for the benchmark group that would not benefit from any intervention.
Child and mother short and long terms healthcare costs related to negative pre-, perinatal and post-partum health outcomes due to tobacco exposure (years in chronic diseases, health costs of perinatal interventions such as e.g. caesarean sections, length of hospital stay both for mother and child, etc) will be included in the analysis.
To estimate the costs of each scenario beyond 2016, we will apply an inflation rate and a discount rate. The inflation rate will be calculated based on health care basket price index. We will apply the recommended discount rate by the WHO, which is currently 3%.

US experiences in illicit drug use disorders: In France, there is neither research, nor clinical care using financial incentives for illicit drug users. We think that US practices cannot be transposed to France; we would like to be as specific as possible that is remain in the field of smoking cessation in pregnancy for which our investigators has highly specific routine expertise.

20 € for adherence: We agree that this is not an incentive. It is important for the control group's adherence to the research protocol. Moreover, rewarding show-up would reduce lost to follow-up and by this, increase power. Evidently, the total sum of incentives in the intervention group will be, as you state, for adhering with both the scheduled visits and being abstinent from smoking,.

I have no further comments and commend Berlin and colleagues on an outstanding and potentially high impact protocol and report.
Response: Thank you for your kind and positive review.

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VERSION 2 – REVIEW

REVIEWER	Assoc Prof Marita Lynagh University of Newcastle Australia
REVIEW RETURNED	13-Apr-2016

GENERAL COMMENTS	I am satisfied that my comments & concerns have been adequately addressed by the authors in their revised manuscript.