BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017321
Article Type:	Protocol
Date Submitted by the Author:	19-Apr-2017

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Health services research, Evidence based practice
Keywords:	Clinical governance < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS

Impact of conditional cash transfer on pregnancy outcomes in underprivileged women: a nationwide pragmatic cluster-randomized clinical trial. The NAITRE study. Protocol publication.

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Abstract

Introduction. Prenatal care is recommended during pregnancy to improve neonatal and maternal outcomes. Women of lower socio-economic status (SES) are less compliant to recommended prenatal care and suffer a higher risk of adverse perinatal outcomes. Several attempts to encourage optimal pregnancy follow-up have shown controversial results, particularly in high-income countries. Few studies have assessed financial incentives to encourage prenatal care, and none reported materno-foetal events as the primary outcome. Our study is aimed to assess if financial incentive can improve pregnancy outcomes in women with low SES.

Methods and analysis. This pragmatic cluster-randomized clinical trial includes pregnant women with the following criteria: i) age above 18 years, ii) first pregnancy visit before 26 weeks of gestation, iii) belonging to a socioeconomically disadvantaged group. Intervention consists in offering financial incentives conditional on attending scheduled pregnancy follow-up consultations. Clusters are 2-month periods with random turnover across centres. A composite outcome of maternal and neonatal morbidity and mortality is the primary endpoint. Secondary endpoints include maternal or neonatal outcomes assessed separately, qualitative assessment of the perception of the intervention, and cost-effectiveness analysis for which children will be followed to the end of their first year through the French health insurance database. The study started in June 2016, and based on an expected decrease in the primary endpoint from 18% to 14% in the intervention group, we plan to include 2000 women in each group.

Ethics and dissemination. Ethics approval was first gained on September 28th 2014. An independent data security and monitoring committee has been established. Results of the main trial and each of the secondary analyses will be submitted for publication in a peer-reviewed journal.

Trial Registration number. NCT02402855.

Strengths and limitations of this study

- Inadequate prenatal care has been associated with poor pregnancy outcomes and in high-income countries socioeconomically disadvantaged women have increased rates of both unattended pregnancy follow-up visits and of pregnancy-related adverse outcomes. Among interventions that aim to promote adequate prenatal care, financial incentives have the potential to overcome some of the barriers, but data on the reality and the magnitude of such an effect on pregnancy outcomes are sparse.
- A cluster randomized clinical trial, using a Zelen design, will run in about 40 public maternity units all over France, with the aim to include a total of 4000 women. The intervention group will receive a €30 incentive for each scheduled prenatal visit they have attended. The control group will be followed according to the national recommendations and local practices.
- The main outcome: a composite of maternal and neonatal adverse outcomes. Secondary outcomes will include qualitative assessment and cost-effectiveness of intervention.
- The definition of the low socioeconomic group relies on type of health-care insurance alone, no individual assessment will be conducted.
- Follow-up of children until their first birthday will only rely on electronic data from the French Health Insurance database

INTRODUCTION

Prenatal care, i.e. the medical and nursing care recommended during pregnancy, aims to prevent, if possible, any potential problems or to detect them early to organise appropriate management of any pregnancy-related condition. A number of studies have demonstrated a relationship between fewer prenatal visits and poorer pregnancy outcomes. A large retrospective cohort in the United States demonstrated that women with inadequate prenatal care (defined as attending fewer than 50% of recommended visits) had an increased risk of preterm birth (OR 2.0, 95% CI 1.9-2.0), low birth-weight (OR 1.7, 95%CI 1.6-1.7), and infant mortality (OR 1.5, 95%CI 1.3-1.7) compared to women who received adequate prenatal follow-up.[1] The same association was described in Finland but the magnitude of the effect was even higher and adverse pregnancy outcomes, such as low birth weight or foetal deaths, persisted even after adjusting for marital status, educational level, maternal age, smoking and alcohol use.[2] In France, inadequate prenatal care has been associated with a 5.8 and 3.3 increased risk of preterm delivery in French and foreign mothers, respectively.[3]

As the provision of prenatal care to pregnant women appears to be an effective way to improve perinatal outcomes, many countries have implemented specific recommendations for this care, with various expectations in different countries, the minimum being four antenatal visits, as recommended by the WHO.

Appropriate pregnancy follow-up is based on early initial access to a health professional and adequate compliance with the scheduled follow-up visits. It has been suggested that initial access is influenced by late recognition of the pregnancy and subsequent denial or acceptance whereas follow-up depends on a strategy of weighing up and balancing out of the perceived gains and losses. Personal resources in terms of time, money and social support as well as the services available are all taken into account.[4]

Perinatal outcomes in socioeconomically disadvantaged populations have been shown to be worse than those in the rest of the population, in terms of perinatal death,[5] prematurity,[6] congenital anomalies, and low birth weight.[7] For example, a population-based study conducted in the UK studied 7,185 preterm

births (between 22 and 32 weeks of amenorrhea [WA]) among 549,618 births, between 1994 and 2003.[8] It showed an association between the child poverty index and the incidence of prematurity: 10.4/1000 preterm births between 22 and 32 WA among the less deprived women versus 16.4/1000 for the more disadvantaged women (adjusted OR 1.94; 95%CI: 1.73-2.17).[8] In a study conducted in the UK, it was shown that social deprivation was an important predictor of infant and perinatal mortality.[9]

Access to prenatal care is insufficient in this at-risk population. This has been demonstrated in countries where access to care is not equal such as the United States, but is also true in countries such as Belgium or France, where free healthcare is provided for socially disadvantaged populations.[10] In France for example preliminary results of the preCARE cohort, that analysed data of about 10000 women, suggested that women covered with insurance for low-income people (CMU for Couverture Maladie Universelle or Universal Medical Coverage) and insurance for illegal immigrants (AME for Aide Médicale d'Etat or State Medical Assistance) have respectively a 50% and 80% increased risk of severe maternal morbidity (Relative Risk of 1.5; 95%CI: 0.95-2.3 and 1.8; IC95% 1.1-3.1, for CMU and AME women respectively, personal data).

In addition, adequate prenatal care has been shown to be cost-effective. This effect is largely due to the extremely high cost of care for preterm and low birth-weight infants. A recently published review of the literature underlined the clear inverse relationship between costs and gestational age at birth, with costs standing at over US$ 100,000 for extreme prematurity, between US$ 40,000 and US$ 100,000 for early prematurity, between US$ 10,000 and US$ 30,000 for moderate prematurity and below US$ 4,500 for late prematurity.[11]

Several interventions to improve pregnancy follow-up have been assessed, and most of the recent literature on this topic has come from low- and middle-income countries. In a systematic review published in 2016, Lassi and colleagues[12] assessed human resources for heath (HRH) and showed that HRH interventions could contribute positively to the health worker's performance and thus improve maternal outcomes. The meta-analysis published in 2015 by the same authors suggested that

community-based intervention packages could lead to a significant reduction in neonatal mortality (RR 0.75, 95% CI 0.67-0.83), and a possible effect on maternal mortality (RR 0.80; 95%CI 0.64-1.00).[13]

In the few studies conducted in high-income countries recently several reinforcement interventions have been tested. A study conducted in the US among primiparous African-American women assessed four levels of incremental interventions, which combined financial support with enhanced post-delivery follow-up.[14] None of these interventions proved to be effective, even as a numerical trend, in reducing premature delivery or the proportion of SGA infants.

More recently, a study conducted in Ireland between 2008 and 2010 recruited women from a disadvantaged community in Dublin and assessed a home-visit program.[15] This program had no impact on any of the neonatal outcomes even though it suggested an increased rate of spontaneous onset of labour and a decreased rate of caesarean deliveries in the intervention group. It is remarkable that in this study only 60% of the prescribed home visits were received, which is in good agreement with the literature on home visits.[15]

Some studies have suggested that the use of incentives may improve prenatal care, and neonatal outcomes. A retrospective cohort study in Canada demonstrated that low-income pregnant women who participated in a prenatal support program beginning early in pregnancy (before 21 weeks of gestation) had significantly decreased rates of low birthweight (LBW) infants compared to women who enrolled later in pregnancy (after 30 weeks of gestation) (risk ratio (RR) 0.47, 95% CI 0.22-0.98).[16]

However, very few data are available from randomized studies. A Cochrane review on this topic was published in 2015.[17] It aimed to determine whether incentives can effectively increase the utilization of timely prenatal care among women. None of the included trials reported any of the primary outcomes of the review, i.e. preterm birth, small for gestational age and perinatal deaths. However, pregnant women receiving incentives were more likely to obtain adequate quality prenatal care (mean difference 5.84, 95%CI 1.88-9.80). This Cochrane review concluded that data from randomized trials, powered to show results on maternal and neonatal outcome, are urgently needed to inform public health authorities.

It has been suggested that incentive programs are effective, for example, for smoking cessation during pregnancy.[18] Nevertheless, this approach remains highly controversial and an article on public acceptability of such programs, published in 2014, concluded that trials evaluating reach, impact on health inequalities and ethnic groups are required prior to implementing incentive interventions.[19]

This paper describes the protocol of an adequately powered cluster-RCT to explore the effectiveness on perinatal outcomes of financial incentives linked to the use of prenatal care and targeting socioeconomically disadvantaged women.

Rationale:

Health professionals and policymakers agree that pregnancy follow-up is suboptimal in socioeconomically disadvantaged women and is associated to an increased risk for adverse pregnancy outcomes. Some studies have suggested that incentive programs, in particular cash-based programs, as suggested in this review and in several observational studies, may increase the frequency of visits and ensure adequate quality of prenatal care.

Objectives:

Primary objectives

The primary objective is to assess the superiority of a conditional cash transfer program in addition to the best standard of care compared with the best standard of care alone among socioeconomically disadvantaged women. The best standard of care is based on the guidelines defined by French health authorities (HAS), and superiority will be assessed in terms of maternal-foetal outcomes.

Secondary objectives

1. To determine whether a conditional cash transfer program can improve neonatal outcomes
2. To determine whether a conditional cash transfer program can improve maternal pregnancy

outcomes.

3. To assess through a qualitative approach, among women of the incentive program group, their acceptance of the program, and whether it has a significant impact on their adherence to prenatal care
4. To assess, among women from both groups, determinants of inadequate prenatal care
5. To assess the cost-effectiveness and budget impact of the conditional cash transfer program compared with the best standard of care without the conditional cash transfer

Methods and Analysis

NAITRE trial design.

The NAITRE study is a pragmatic multi-centre, open-label cluster-randomized trial using a parallel arm design.

During year one of the study, June 2016 to June 2017, 10 centres, all tertiary obstetric departments, are including women. These centres are located throughout France. Starting in June 2017 the study will be extended to about 30 additional primary to tertiary Obstetric departments, assuming the qualitative study shows no negative feeling of the patients (see specific section below).

The cluster randomization procedure was chosen in order to allow a Zelen design,[20] i.e. women being randomized before they consent to participate, and only receiving information for the group they will be allocated to. This is of particular relevance as when patients do not receive their preferred treatment in randomized trials, there may be difficulties with patient recruitment and scientific problems with bias. Centres, and not women, are being randomized. To account for heterogeneity among centres and the relatively small number of centres, about 40, clusters are 2-month periods with random turnover across centres, meaning that each centre will contribute both to the intervention and the control groups.

Patient enrolment started in June 2016 and is expected to end in December 2018.

The study was approved by a central ethics committee (Comité de Protection des Personnes Est-1), by

the French Medicines Agency, and data collection and recording was approved by the CNIL (Commission Informatique et liberté).

Figure 1 summarizes the design of the trial and each aspect of the trial is described in detail below.

Eligibility criteria:

The study includes pregnant women: 1) above the age of 18, 2) with their first pregnancy visit in one of the participating centres before the end of the 26th week of amenorrhea, 3) with social insurance for low-income people (CMU for Universal Medical Coverage) or illegal immigrant status (AME for Aide Médicale d'Etat or State Medical Insurance)

The only non-inclusion criteria are: 1) women not able to understand the study, 2) under legal supervision. There are no other restrictions to the inclusion criteria as the study has a pragmatic concept.

Randomization.

Centres are randomly allocated to two-month periods of either the intervention or control group. Randomization is centrally generated, and before the end of a period centres are not aware of the group they will be allocated to for the next period, in order to prevent the postponement of inclusions at the end of one control period so as to include women in the next intervention period.

The inclusion of patients and the reporting of further pregnancy follow-up visits are made through a web-based eCRF (www.etudenaitre.fr), where the information sheet and consent form, translated in 18 foreign languages, can be directly downloaded. Women will be included prospectively by obstetricians and midwifes in the participating centres, based on their type of health insurance coverage

Treatments arms.

Control group:

Women in the control group receive prenatal care according to the standard practice, as set out in national guidelines. Women's personal medical history and pregnancy medical data are collected up to one month post discharge after delivery whereas data for their child will be collected up to their first birthday.

Intervention group

Women in the intervention group are given a payment card on their first visit, the inclusion visit. The card will be credited with €30 after each scheduled prenatal visit, with a maximum of one €30 incentive per month. Cash transfer starts at the first scheduled visit after the inclusion visit.

No additional incentives will be provided if more visits are deemed necessary because of a specific pregnancy follow-up program, or unplanned visit at the emergency department. Inclusion using the eCRF automatically generates the scheduled prenatal visits program according to the national guidelines. *Figure one* shows the agenda for prenatal visits with time windows for incentives.

Outcomes

Primary outcome

The primary endpoint is a global composite endpoint of perinatal morbidity and mortality, defined as the occurrence of at least one complication of pregnancy, whether maternal, foetal or neonatal.

- For infants: perinatal death, premature birth (before 37 weeks of amenorrhea), intrauterine growth restriction (estimated weight < the 10th percentile for gestational age and abdominal circumference below the 2.5th percentile), low birth weight (<2500g at term), early neonatal encephalopathy (asphyxia at birth and cerebral anomalies of neonatal or perinatal origin (anoxic or ischemic encephalopathy, periventricular leukomalacia or intraventricular haemorrhage), lesion of the brachial plexus (clinical diagnosis), probable or certain maternal-foetal infection (clinical and biological diagnosis). Birth of a child with a congenital abnormality is considered a failure if it results

from a lack of prenatal diagnosis, but a success if it results from parental choice. Therapeutic interruptions of pregnancy for congenital malformation diagnosed during pregnancy are likewise considered part of the optimal follow-up and are counted as successes.

- For the mother: maternal death, phlebitis, pulmonary embolism (diagnosed by Doppler ultrasound of the lower limbs and/or spiral scan and/or pulmonary scintigraphy), pre-eclampsia or eclampsia, postpartum haemorrhage requiring transfusion, conservative surgery or embolization of uterine arteries or hysterectomy, postpartum endometritis (clinical diagnosis), 3rd or 4th degree perineal lesion with anal sphincter injury.

Perinatal outcomes will be assessed at hospital discharge of both the mother and the infant (last discharged).

Secondary outcomes

1. Adverse perinatal outcome in the child, as previously defined.
2. Adverse perinatal outcome in the mother, as previously defined.
3. Number of prenatal consultations following the French standard care recommendations. All outpatient visits, including those prospectively scheduled by the study protocol, will be retrieved using the French Health Insurance database (SNIIR-AM)
4. Qualitative assessment of barriers to adequate prenatal follow-up and the perception of the intervention by some of the participating women and health professionals.
5. Differential cost-effectiveness ratio associated with financial incentive versus no compensation and expressed in terms of cost per complication avoided.
6. Overall budget impact

Cost-effectiveness analysis

Study design

A cost-effectiveness analysis comparing the financial incentive strategy associated with prenatal care of socio-economically disadvantaged women versus no financial incentive will be carried out. The reference strategy is standard prenatal care in the absence of financial incentives.

This analysis will be conducted from a societal perspective in such a way as to favour a sufficiently broad perspective to take into account all stakeholders involved in the intervention.

Outcomes

Efficacy is a composite criterion that includes complications of the child during his/her first year of life (such as perinatal death, prematurity or neurological impairment) and maternal adverse events (including post-partum haemorrhage, endometritis). Direct costs will be considered from a societal perspective. The effectiveness of the intervention will be expressed in terms of cost per complication avoided. The time horizon of the study will be at most one year and nine months, corresponding to the period of pregnancy and a one-year post-delivery follow-up period. Given the relatively short duration of follow-up, costs and effectiveness will not be updated. In addition to data collected in the CRF, all direct medical costs up to one year post-delivery will be retrieved from the National Health Insurance database.

Qualitative assessment method.

Practical aspects

Patients will be selected after delivery according to their medical follow-up during pregnancy. Only patients with no complications during pregnancy or during childbirth will be selected so that these events do not affect the results obtained.

Semi-directed individual interviews will aim to understand the determinants of medical follow-up

during pregnancy. The principle is to get the respondents to describe situations that highlight their habits, their social representations or their emotions. Women will be asked to describe their health practices during pregnancy, what was important for their medical follow-up, what led them to renounce scheduled care. For women who received the financial incentive, it is also a question of asking them how they experienced this incentive and what it may or may not have brought them.

Interviews will take place within one month of delivery. Patients will be invited to return to the referral centre (with a specific incentive of €40 credited to the card for those in the intervention group, or a payment card for those in the control group).

The method of semi-structured individual interviewing is based on an interview grid containing closed or open questions, designed so as not to be inductive with regard to the themes to be explored. Interviews will begin with an open-ended question: "*Can you tell me about the medical follow-up of your pregnancy*?".

Depending on the construction of the interviewee's story and according to the logic of a dialogue, questions will be asked so as to get the person to answer the questions of the survey if the information has not been provided spontaneously. These questions will be grouped in an interview grid available to the interviewer at the time of the interview with the respondent. These interview grids are constructed in such a way so as to favour a more or less long interview depending on the interviewee (about 1 hour), using simple, easily understandable questions.

Whenever necessary, the interview will be conducted with the assistance of an interpreter (telephone interpreter, planned budget).

Method of collection

The respondents will be met individually in a confidential location. Interviews will be conducted by a social scientist trained in qualitative research. Women will be asked to allow the interview to be recorded, transcribed and analysed anonymously.

Study sample

All eligible women registering for maternity care at the trial sites during the study period will be invited to participate in the study. The list of the participating centres can be found on ClinicalTrials.gov (NCT02402855).

According to the 2010 French perinatal survey, the estimated prevalence of adverse pregnancy outcomes, according to our primary outcome definition is estimated at 12% in the general population and 18% in socioeconomically disadvantaged women.[21] The hypothesis supporting our sample size calculation is that the financial incentive, by increasing adherence to prenatal care, can reduce this difference by two-thirds, thus resulting in a rate of complicated pregnancies in the intervention group of 14%. To ensure a power of 80% and an alpha-risk of 0.05, 1,314 patients per group are needed.

In order to obtain accurate data, the frequency of randomization was set at every two months. According to the randomisation procedure, we will have 420 clusters (2 months periods in over 3 years for the 10 participating maternity departments of the first phase and over 2 years in the up to 30 additional centres included in second phase) and about 8 women by cluster.

We hypothesized a correlation coefficient of 0.01, necessitating 1,526 patients.[22] Allowing for 20% attrition, 1,900 patients per group were needed, and we set the sample size at 2,000 per group.

Statistical analysis

All data analyses will be conducted by a statistician blinded to allocation to the intervention group.

Data will be extracted from individual pregnancy records, in each of the participating centre, and collected into the electronic Case Report Form by clinical research assistant.

For the cost-effectiveness study, data for the first year of life will be extracted from the French Hospitalisation (PMSI) and Health Insurance (SNIIR-AM) databases, and analysed in Dijon University Health Centre

Descriptive analysis

Clinical and demographic characteristics of the patients will be presented, and the comparability of the two groups of patients regarding pregnancy risk factors will be assessed.

Primary outcome analysis

The primary criterion, as described previously, is binary. The principal analysis will be a proportion comparison using the Chi-squared test adjusted for the design effect, on an individual basis.

The cluster randomization ensuring a lower quality of the balance of the covariates, we will additionally study the following parameters, which potentially interfere with maternal or foetal outcomes, using univariate logistic regression:

- type of centre (local / intermediate risk / high-risk maternity unit)
- proportion of deprived patients in the centre (three levels defined as $<25^{th}$, 25^{th} -75^{th} and $>75^{th}$ percentile of the observed proportions in the different centres)
- age (<20, 20-35, >35 years old)
- parity (0, 1 or 2, more than 2)
- type of free healthcare (CMU-C/AME)

Interaction of these parameters and the effect of the intervention will be searched for using sub-group analyses.

A multivariate multilevel logistic regression adjusted for all the covariates with a $p<0.20$ will then be performed, taking into account the eventual interactions, the cluster being affected a random effect level.

Secondary outcome analysis

1. Adverse outcomes in the child: same as the principal analysis, using this outcome.

2. Adverse outcomes in the mother: same as the principal analysis, using this outcome.

3. The number of prenatal consultations following the HAS standard care recommendations will be analysed using weighted means taking into account the cluster randomization.

An intermediate analysis will be performed after the first phase, but using a significance level of 0.0001 in order not to impair the study power.

Significance threshold

The results will be considered statistically significant if $p<0.05$.

Statistical software

The analyses will be performed using SAS software, latest version at the time of analysis. Statistician will be blinded for the study groups

Analysis of qualitative survey.

It follows the logic of anchored theory based on empirical data from which a theory is constructed.[23] Raw data are thus analysed according to a thematic analysis method. From this progressive work of conceptualization and continuous comparison of the different situations, a theoretical system responding to our problems will be defined. Nvivo software, which allows the creation of a code, and has been well validated for qualitative analyses will be used.[24]

Statistical analysis of cost effectiveness.

A differential cost-effectiveness ratio associated with the intervention versus no intervention will be calculated by comparing the difference in average costs with the difference in average efficiencies. In order to test the robustness of the conclusions drawn, sensitivity analyses will be carried out on the parameters likely to have an influence on the results.

A nonparametric bootstrap analysis of the cost and efficiency differential observed between the two strategies will allow uncertainty to be taken into account and to estimate 95% confidence intervals for the differential ratios of the baseline analysis.

Data and Safety Monitoring Committees:

The data will be managed by the Clinical Investigation Centre (CIC INSERM 1432) at Dijon University Hospital.

The steering committee is composed of the principal investigators of the first 10 centres, one representative from each perinatal care network involved in the study, a midwife, a social worker and a methodologist. A phone meeting will be held every four months.

The scientific committee will be composed of two obstetricians specifically taking care of socioeconomically disadvantaged women, a methodologist, an ethics specialist, and a paediatrician. The scientific committee will essentially review results of qualitative survey conducted during the first year. If the qualitative survey were to suggest that intervention stigmatize women, the scientific committee will have the right to stop the study.

Monitoring

The study will be monitored for quality and regulatory compliance. The monitoring will be supervised by the promoter (Dijon University Hospital) in all of the participating centres. The frequency depends on inclusion rates, questions and pending issues from earlier audits: once or twice a year.

Figure 2 shows the overall management of women included in the study according to the group of randomisation

Ethics and dissemination

Ethics approval was given by the Dijon ethics committee (CPP Est-1) on September 18th 2014, and the protocol was amended thereafter.

The study is funded by the French Ministry for Health in December 2014 (PREPS-14-0173) and

promoted by Dijon Bourgogne University Hospital (France).

Authorization for holding the computerized databases was granted on March 21st 2016 by the National Committee for Informatics and Freedom (CNIL). This long delay was due to conflict between the reasoning of the CNIL, for which the preservation of private life is its top priority, and the French source of public funding, which needs to know precisely to whom public money, in this case the financial incentive, is being given.

It was registered in Clinicaltrials.gov with the identifier NCT02402855, on March 17th, 2015, at the French Research Agency with identifier 2014-A01319-38, and at the CNIL with request for authorization n°915385.

A manuscript with the results of the primary study will be published in a peer-reviewed journal. Separate manuscripts will be written on each of the secondary aims, and these will also be submitted for publication in peer-reviewed journals.

Recruitment is on-going; the first patients were recruited on June 4th 2016 in the control group and on June 10th 2016 in the intervention group.

Discussion.

This will be the first study to provide rigorous evidence regarding the effectiveness of financial incentives, to improve the use of prenatal care, on perinatal outcomes for the mother and the foetus. A recent Cochrane meta-analysis,[17] emphasized the need for such an assessment, and it is of particular interest to note that no such studies have been carried in Europe so far.

The conditional cash-transfer is not supposed to replace any other public health policies aimed to promote appropriate prenatal care but it may help to overcome some of the barriers that stand in the way of adequate follow-up. Most of the studies have been conducted in low-income countries, where, besides many other factors, the structure of the health care system and health care facilities are very different from those in developed Countries.

For example, in 2005, the Indian Government implemented the Janani Suraksha Yojana program, which incentivizes poor women to give birth in a health facility by providing them with a cash transfer upon discharge. There was, however, no formal assessment of the efficacy. Whereas this program was associated with a very significant increase in the rate of delivery in health care facilities (from 39% to 74%), a recent survey suggested that beyond the cash incentive, the shift in the social norm and the women's own perception played a major role in this effect.[25] Interestingly, this program was shown to be associated with a reduction in neonatal and perinatal deaths.[26]

Financial incentive programs to promote smoking cessation during pregnancy have been assessed and have recently been reported to be associated with a reduced odds of low-birth weight.[27]

If our intervention proves to be effective, its implementation may have to overcome several difficulties, including tailoring the intervention to women most likely to respond, increasing acceptability of the concept among public bodies and health professionals, and proving the intervention to be cost effective. It has been suggested that for some interventions, efforts have to be made to increase acceptability, even when they have been proven to be effective.[28] All of these aspects will be covered by our research program.

The investigators have no conflicts of interest to declare.

***NAITRE study group:**

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B. competing interests

Authors of the present paper have no competing interest to disclose.

C. funding:

The study has been funded by the French Ministry for Health, Health Offer General Direction (reference number PREPS-14-0173).

D. data sharing statement:

Authors have no data to share at this stage.

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Figure legends.

Figure 1. Scheduled prenatal care visit and time window for financial incentives. If a women shows up for a scheduled more than 2 weeks after her standard pre planned agenda, she will receive the incentive for the next visit. It means that she won't attend a scheduled visit without receiving an incentive (with the limit of no more than one incentivised visit per month), but she may receive less incentive that the maximum she could have had access to.

Figure 2. Overall management of women, according to their group of allocation. CRA = Clinical Research Assistant.

Bardou et al. figure 1

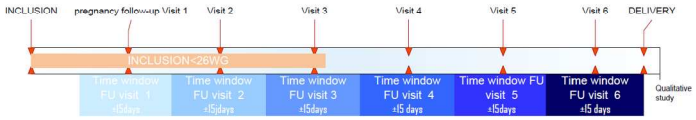

Figure 1

254x190mm (196 x 196 DPI)

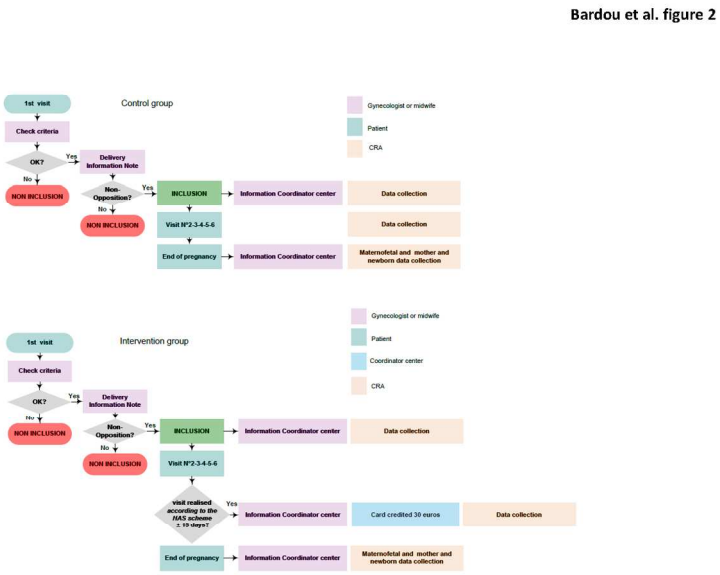

Figure 2

254x190mm (175 x 175 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	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5-8
	2b	Specific objectives or hypotheses	8-9
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9-10
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	15
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			18
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
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	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	17

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	15-17
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	15-17
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	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
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)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	3 and 19
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	18 and 21

*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.

BMJ Open

The NAITRE study - Impact of conditional cash transfer on poor pregnancy outcomes in underprivileged women: protocol for a nationwide pragmatic cluster-randomized superiority clinical trial in France.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017321.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Jul-2017

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Health services research, Evidence based practice, Health policy
Keywords:	Clinical governance < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS

The NAITRE study - Impact of conditional cash transfer on poor pregnancy outcomes in underprivileged women: protocol for a nationwide pragmatic cluster-randomized superiority clinical trial in France.

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Abstract

Introduction. Prenatal care is recommended during pregnancy to improve neonatal and maternal outcomes. Women of lower socio-economic status (SES) are less compliant to recommended prenatal care and suffer a higher risk of adverse perinatal outcomes. Several attempts to encourage optimal pregnancy follow-up have shown controversial results, particularly in high-income countries. Few studies have assessed financial incentives to encourage prenatal care, and none reported materno-foetal events as the primary outcome. Our study is aimed to assess if financial incentive can improve pregnancy outcomes in women with low SES in a high-income country.

Methods and analysis. This pragmatic cluster-randomized clinical trial includes pregnant women with the following criteria: i) age above 18 years, ii) first pregnancy visit before 26 weeks of gestation, iii) belonging to a socioeconomically disadvantaged group. Intervention consists in offering financial incentives conditional on attending scheduled pregnancy follow-up consultations. Clusters are 2-month periods with random turnover across centres. A composite outcome of maternal and neonatal morbidity and mortality is the primary endpoint. Secondary endpoints include maternal or neonatal outcomes assessed separately, qualitative assessment of the perception of the intervention, and cost-effectiveness analysis for which children will be followed to the end of their first year through the French health insurance database. The study started in June 2016, and based on an expected decrease in the primary endpoint from 18% to 14% in the intervention group, we plan to include 2000 women in each group.

Ethics and dissemination. Ethics approval was first gained on September 28th 2014. An independent data security and monitoring committee has been established. Results of the main trial and each of the secondary analyses will be submitted for publication in a peer-reviewed journal.

Trial Registration number. NCT02402855 (March 17 2015) (. Protocol version 5, June 30, 2016)

Strengths and limitations of this study

- Inadequate prenatal care has been associated with poor pregnancy outcomes and in high-income countries socioeconomically disadvantaged women have increased rates of both unattended pregnancy follow-up visits and of pregnancy-related adverse outcomes. Among interventions that aim to promote adequate prenatal care, financial incentives have the potential to overcome some of the barriers, but data on the reality and the magnitude of such an effect on pregnancy outcomes are sparse.
- A cluster randomized clinical trial, using a Zelen design, will run in about 40 public maternity units all over France, with the aim to include a total of 4000 women. The intervention group will receive a €30 incentive for each scheduled prenatal visit they have attended. The control group will be followed according to the national recommendations and local practices.
- The main outcome: a composite of maternal and neonatal adverse outcomes. Secondary outcomes will include qualitative assessment and cost-effectiveness of intervention.
- The definition of the low socioeconomic group relies on type of health-care insurance alone, no individual assessment will be conducted.
- Follow-up of children until their first birthday will only rely on electronic data from the French Health Insurance database

INTRODUCTION

Background and rationale. Prenatal care, i.e. the medical and nursing care recommended during pregnancy, aims to prevent, if possible, any potential problems or to detect them early to organise appropriate management of any pregnancy-related condition. A number of studies have demonstrated a relationship between fewer prenatal visits and poorer pregnancy outcomes. A large retrospective cohort in the United States demonstrated that women with inadequate prenatal care (defined as attending fewer than 50% of recommended visits) had an increased risk of preterm birth (OR 2.0, 95% CI 1.9-2.0), low birth-weight (OR 1.7, 95%CI 1.6-1.7), and infant mortality (OR 1.5, 95%CI 1.3-1.7) compared to women who received adequate prenatal follow-up.[1] The same association was described in Finland but the magnitude of the effect was even higher and adverse pregnancy outcomes, such as low birth weight or foetal deaths, persisted even after adjusting for marital status, educational level, maternal age, smoking and alcohol use.[2] In France, inadequate prenatal care has been associated with a 5.8 and 3.3 increased risk of preterm delivery in French and foreign mothers, respectively.[3]

As the provision of prenatal care to pregnant women appears to be an effective way to improve perinatal outcomes, many countries have implemented specific recommendations for this care, with various expectations in different countries, the minimum being eight antenatal contacts, as recommended by the WHO.[4]

Appropriate pregnancy follow-up is based on early initial access to a health professional and adequate compliance with the scheduled follow-up visits. It has been suggested that initial access is influenced by late recognition of the pregnancy and subsequent denial or acceptance whereas follow-up depends on a strategy of weighing up and balancing out of the perceived gains and losses. Personal resources in terms of time, money and social support as well as the services available are all taken into account.[5]

Perinatal outcomes in socioeconomically disadvantaged populations have been shown to be worse than those in the rest of the population, in terms of perinatal death,[6] prematurity,[7] congenital anomalies, and low birth weight.[8] For example, a population-based study conducted in the UK studied 7,185 preterm

births (between 22 and 32 weeks of amenorrhea [WA]) among 549,618 births, between 1994 and 2003.[9] It showed an association between the child poverty index and the incidence of prematurity: 10.4/1000 preterm births between 22 and 32 WA among the less deprived women versus 16.4/1000 for the more disadvantaged women (adjusted OR 1.94; 95%CI: 1.73-2.17).[9] In a study conducted in the UK, it was shown that social deprivation was an important predictor of infant and perinatal mortality.[10]

In addition to poverty other social determinant, such as familial structure, community factors such as crime, poverty, housing, and the racial/ethnic makeup of the community, have been associated with pregnancy outcome.[11 12] Access to prenatal care is insufficient in this at-risk population. This has been demonstrated in countries where access to care is not equal such as the United States, but is also true in countries such as Belgium or France, where free healthcare is provided for socially disadvantaged populations.[13] In France for example preliminary results of the preCARE cohort, that analysed data of about 10000 women, suggested that women covered with insurance for low-income people (CMU for Couverture Maladie Universelle or Universal Medical Coverage) and insurance for illegal immigrants (AME for Aide Médicale d'Etat or State Medical Assistance) have respectively a 50% and 80% increased risk of severe maternal morbidity (Relative Risk of 1.5; 95%CI: 0.95-2.3 and 1.8; IC95% 1.1-3.1, for CMU and AME women respectively, personal data).

In addition, adequate prenatal care has been shown to be cost-effective. This effect is largely due to the extremely high cost of care for preterm and low birth-weight infants. A recently published review of the literature underlined the clear inverse relationship between costs and gestational age at birth, with costs standing at over US$ 100,000 for extreme prematurity, between US$ 40,000 and US$ 100,000 for early prematurity, between US$ 10,000 and US$ 30,000 for moderate prematurity and below US$ 4,500 for late prematurity.[14]

Several interventions to improve pregnancy follow-up have been assessed, and most of the recent literature on this topic has come from low- and middle-income countries. In a systematic review published in 2016, Lassi and colleagues[15] assessed human resources for heath (HRH) and showed that

HRH interventions could contribute positively to the health worker's performance and thus improve maternal outcomes. The meta-analysis published in 2015 by the same authors suggested that community-based intervention packages could lead to a significant reduction in neonatal mortality (RR 0.75, 95% CI 0.67-0.83), and a possible effect on maternal mortality (RR 0.80; 95%CI 0.64-1.00).[16]

In the few studies conducted in high-income countries recently several reinforcement interventions have been tested. A study conducted in the US among primiparous African-American women assessed four levels of incremental interventions, which combined financial support with enhanced post-delivery follow-up.[17] None of these interventions proved to be effective, even as a numerical trend, in reducing premature delivery or the proportion of SGA infants.

More recently, a study conducted in Ireland between 2008 and 2010 recruited women from a disadvantaged community in Dublin and assessed a home-visit program.[18] This program had no impact on any of the neonatal outcomes even though it suggested an increased rate of spontaneous onset of labour and a decreased rate of caesarean deliveries in the intervention group. It is remarkable that in this study only 60% of the prescribed home visits were received, which is in good agreement with the literature on home visits.[18] Nevertheless a meta-analysis published in 2016 by Sandal J and colleagues suggests that suggests that women who received midwife-led continuity models of care were less likely to experience intervention preterm birth less than 37 weeks (average RR 0.76, 95% CI 0.64 to 0.91) and less all fetal loss before and after 24 weeks plus neonatal death (average RR 0.84, 95% CI 0.71 to 0.99) than women who received other models of care.[19]

Some studies have suggested that the use of incentives may improve prenatal care, and neonatal outcomes. A retrospective cohort study in Canada demonstrated that low-income pregnant women who participated in a prenatal support program beginning early in pregnancy (before 21 weeks of gestation) had significantly decreased rates of low birthweight (LBW) infants compared to women who enrolled later in pregnancy (after 30 weeks of gestation) (risk ratio (RR) 0.47, 95% CI 0.22-0.98).[20]

However, very few data are available from randomized studies. A Cochrane review on this topic was

published in 2015.[21] It aimed to determine whether incentives can effectively increase the utilization of timely prenatal care among women. None of the included trials reported any of the primary outcomes of the review, i.e. preterm birth, small for gestational age and perinatal deaths. However, pregnant women receiving incentives were more likely to obtain adequate quality prenatal care (mean difference 5.84, 95%CI 1.88-9.80). This Cochrane review concluded that data from randomized trials, powered to show results on maternal and neonatal outcome, are urgently needed to inform public health authorities. It has been suggested that incentive programs are effective, for example, for smoking cessation during pregnancy.[22] Nevertheless, this approach remains highly controversial and an article on public acceptability of such programs, published in 2014, concluded that trials evaluating reach, impact on health inequalities and ethnic groups are required prior to implementing incentive interventions.[23]

This paper describes the protocol of an adequately powered cluster-RCT to explore the effectiveness on perinatal outcomes of financial incentives linked to the use of prenatal care and targeting socioeconomically disadvantaged women.

Health professionals and policymakers agree that pregnancy follow-up is suboptimal in socioeconomically disadvantaged women and is associated to an increased risk for adverse pregnancy outcomes. Some studies have suggested that incentive programs, in particular cash-based programs, as suggested in this review and in several observational studies, may increase the frequency of visits and ensure adequate quality of prenatal care.

Objectives:

Primary objectives

The primary objective is to assess the superiority of a conditional cash transfer program in addition to the best standard of care compared with the best standard of care alone among socioeconomically disadvantaged women. The best standard of care is based on the guidelines defined by French health authorities (HAS), and superiority will be assessed in terms of maternal-foetal outcomes.

Secondary objectives

1. To determine whether a conditional cash transfer program can improve neonatal outcomes
2. To determine whether a conditional cash transfer program can improve maternal pregnancy outcomes.
3. To assess through a qualitative approach, among women of the incentive program group, their acceptance of the program, and whether it has a significant impact on their adherence to prenatal care
4. To assess, among women from both groups, determinants of inadequate prenatal care
5. To assess the cost-effectiveness and budget impact of the conditional cash transfer program compared with the best standard of care without the conditional cash transfer

Trial design.

The NAITRE study is a pragmatic multi-centre, open-label cluster-randomized trial using a parallel arm design.

Methods: Participants, interventions, outcomes

Study setting

During year one of the study, June 2016 to June 2017, 10 centres, all tertiary obstetric departments, are including women. These centres are located throughout France. Starting in June 2017 the study will be extended to about 30 additional primary to tertiary Obstetric departments, assuming the qualitative study shows no negative feeling of the patients (see specific section below).

The cluster randomization procedure was chosen in order to allow a Zelen design,[24] i.e. women being randomized before they consent to participate, and only receiving information for the group they will

be allocated to. This is of particular relevance as when patients do not receive their preferred treatment in randomized trials, there may be difficulties with patient recruitment and scientific problems with bias. Centres, and not women, are being randomized. To account for heterogeneity among centres and the relatively small number of centres, about 40, clusters are 2-month periods with random turnover across centres, meaning that each centre will contribute both to the intervention and the control groups. Patient enrolment started in June 2016 and is expected to end in June 2019.

The study was approved by a central ethics committee (Comité de Protection des Personnes Est-1), by the French Medicines Agency, and data collection and recording was approved by the CNIL (Commission Informatique et liberté).

Figure 1 summarizes the design of the trial and each aspect of the trial is described in detail below.

Eligibility criteria:

The study includes pregnant women: 1) above the age of 18, 2) with their first pregnancy visit in one of the participating centres before the end of the 26th week of amenorrhea, 3) with social insurance for low-income people (CMU for Universal Medical Coverage) or illegal immigrant status (AME for Aide Médicale d'Etat or State Medical Insurance)

The only non-inclusion criteria are: 1) women not able to understand the study, 2) under legal supervision. There are no other restrictions to the inclusion criteria as the study has a pragmatic concept.

Interventions.

Control group:

Women in the control group receive prenatal care according to the standard practice, as set out in national guidelines. Women's personal medical history and pregnancy medical data are collected up to one month post discharge after delivery whereas data for their child will be collected up to their first

birthday.

Intervention group

Women in the intervention group are given a payment card on their first visit, the inclusion visit. The card will be credited with €30 after each scheduled prenatal visit, with a maximum of one €30 incentive per month. Cash transfer starts at the first scheduled visit after the inclusion visit.

No additional incentives will be provided if more visits are deemed necessary because of a specific pregnancy follow-up program, or unplanned visit at the emergency department. Inclusion using the eCRF automatically generates the scheduled prenatal visits program according to the national guidelines. *Figure one* shows the agenda for prenatal visits with time windows for incentives.

Outcomes

Primary outcome

The primary endpoint is a global composite endpoint of perinatal morbidity and mortality, defined as the occurrence of at least one complication of pregnancy, whether maternal, foetal or neonatal.

- For infants: perinatal death, premature birth (before 37 weeks of amenorrhea), intrauterine growth restriction (estimated weight < the 10th percentile for gestational age and abdominal circumference below the 2.5th percentile), low birth weight (<2500g at term), early neonatal encephalopathy (asphyxia at birth and cerebral anomalies of neonatal or perinatal origin (anoxic or ischemic encephalopathy, periventricular leukomalacia or intraventricular haemorrhage), lesion of the brachial plexus (clinical diagnosis), probable or certain maternal-foetal infection (clinical and biological diagnosis). Birth of a child with a congenital abnormality is considered a failure if it results from a lack of prenatal diagnosis, but a success if it results from parental choice. Therapeutic interruptions of pregnancy for congenital malformation diagnosed during pregnancy are likewise considered part of the optimal follow-up and are counted as successes.

- For the mother: maternal death, phlebitis, pulmonary embolism (diagnosed by Doppler ultrasound of the lower limbs and/or spiral scan and/or pulmonary scintigraphy), pre-eclampsia or eclampsia, postpartum haemorrhage requiring transfusion, conservative surgery or embolization of uterine arteries or hysterectomy, postpartum endometritis (clinical diagnosis), 3rd or 4th degree perineal lesion with anal sphincter injury.

Perinatal outcomes will be assessed at hospital discharge of both the mother and the infant (last discharged).

Secondary outcomes

1. Adverse perinatal outcome in the child, as previously defined.
2. Adverse perinatal outcome in the mother, as previously defined.
3. Number of prenatal consultations following the French standard care recommendations. All outpatient visits, including those prospectively scheduled by the study protocol, will be retrieved using the French Health Insurance database (SNIIR-AM)
4. Qualitative assessment of barriers to adequate prenatal follow-up and the perception of the intervention by some of the participating women and health professionals.
5. Differential cost-effectiveness ratio associated with financial incentive versus no compensation and expressed in terms of cost per complication avoided.
6. Overall budget impact

Participant timelines.

Women will be followed according to official antenatal care program, and to their obstetrician request. No additional visit or test of any type will be requested because of their participation in the trial. Data will be recorded from inclusion to discharge from the maternity ward.

New-borns will be followed up to discharge from hospital.

For the cost-effectiveness study, data on health resources utilisation, i.e. outpatient clinics, blood or imaging tests performed and mediation purchased will be collected through the national health insurance database, up to the first year of age for the children.

Figure 2 shows the overall management of women included in the study according to the group of randomisation

Sample Size

According to the 2010 French perinatal survey, the estimated prevalence of adverse pregnancy outcomes, according to our primary outcome definition is estimated at 12% in the general population and 18% in socioeconomically disadvantaged women.[25] The hypothesis supporting our sample size calculation is that the financial incentive, by increasing adherence to prenatal care, can reduce this difference by two-thirds, thus resulting in a rate of complicated pregnancies in the intervention group of 14%. To ensure a power of 80% and an significance level of 0.05, 1,314 patients per group are needed.

In order to obtain accurate data, the frequency of randomization was set at every two months. According to the randomisation procedure, we will have 420 clusters (2 months periods in over 3 years for the 10 participating maternity departments of the first phase and over 2 years in the up to 30 additional centres included in second phase) and about 8 women by cluster.

We hypothesized an intraluster correlation coefficient (ICC) of 0.01, necessitating 1,526 patients.[26] Allowing for 20% attrition, 1,900 patients per group were needed, and we set the sample size at 2,000 per group. An ICC of 0.01 was selected because the trial assesses an intervention aimed directly at the patient and an outcome measurement for which the variance between practices is low compared with the variability between patients within a practice.

Recruitment

All eligible women registering for maternity care at the trial sites during the study period will be invited to participate in the study. The list of the participating centres can be found on ClinicalTrials.gov (NCT02402855).

Cost-effectiveness analysis

Study design

A cost-effectiveness analysis comparing the financial incentive strategy associated with prenatal care of socio-economically disadvantaged women versus no financial incentive will be carried out. The reference strategy is standard prenatal care in the absence of financial incentives.

This analysis will be conducted from a societal perspective in such a way as to favour a sufficiently broad perspective to take into account all stakeholders involved in the intervention.

Outcomes

Efficacy is a composite criterion that includes complications of the child during his/her first year of life (such as perinatal death, prematurity or neurological impairment) and maternal adverse events (including post-partum haemorrhage, endometritis). Direct costs will be considered from a societal perspective. The effectiveness of the intervention will be expressed in terms of cost per complication avoided. The time horizon of the study will be at most one year and nine months, corresponding to the period of pregnancy and a one-year post-delivery follow-up period. Given the relatively short duration of follow-up, costs and effectiveness will not be updated. In addition to data collected in the CRF, all direct medical costs up to one year post-delivery will be retrieved from the National Health Insurance database.

Qualitative assessment method.

Practical aspects

Patients will be selected after delivery according to their medical follow-up during pregnancy.

Every woman included into the NAITRE study is eligible for the qualitative study except in case of stillbirth, postnatal death or if the baby suffers seriously condition. As the women should be in position to relate their pregnancy, it seems it would be difficult for patients in mourning.

To ensure an adequate representativeness, women will be selected both in the intervention and in the control group, different ages, primiparous and multiparous, different type of economic conditions, adherence to prenatal care. These information are given by investigators after the delivery. Semi-directed individual interviews will aim to understand the determinants of medical follow-up during pregnancy. The principle is to get the respondents to describe situations that highlight their habits, their social representations or their emotions. Women will be asked to describe their health practices during pregnancy, what was important for their medical follow-up, what led them to renounce scheduled care. For women who received the financial incentive, it is also a question of asking them how they experienced this incentive and what it may or may not have brought them.

In order to get these information, a retrospective study will be conducted. Interviews will take place within one month of delivery. Patients will be invited to return to the referral centre or will be seen at their home (with a specific incentive of €40 credited to the card for those in the intervention group, or a payment card for those in the control group).

The method of semi-structured individual interviewing is based on an interview guide containing closed or open questions, designed so as not to be inductive with regard to the themes to be explored. Interviews will begin with an open-ended question: "*Can you tell me about your pregnancy*?".

Depending on the construction of the interviewee's story and according to the logic of a dialogue, the questions of the interview guide will be asked sonly if the information has not been provided spontaneously. These questions will be grouped in an interview guide available to the interviewer at the time of the interview with the respondent. These interview guides are constructed in such a way so as to favour a more or less long interview depending on the interviewee (about 1 hour), using simple,

easily understandable questions.

Whenever necessary, the interview will be conducted with the assistance of an interpreter (telephone interpreter, planned budget).

Method of collection

The respondents will be met individually in a confidential location. Interviews will be conducted by a social scientist trained in qualitative research. Women will be asked to allow the interview to be recorded, transcribed and analysed anonymously.

Methods: assignment of intervention

Allocation.

Centres are randomly allocated to two-month periods of either the intervention or control group. Randomization is centrally generated, and before the end of a period centres are not aware of the group they will be allocated to for the next period, in order to prevent the postponement of inclusions at the end of one control period so as to include women in the next intervention period.

The inclusion of patients and the reporting of further pregnancy follow-up visits are made through a web-based eCRF (www.etudenaitre.fr), where the information sheet and consent form, translated in 18 foreign languages, can be directly downloaded. Women will be included prospectively by obstetricians and midwifes in the participating centres, based on their type of health insurance coverage

Blinding

By nature blinding of the intervention is not feasible. But all analyses will be conducted by a statistician blinded to allocation to the intervention group.

Methods: Data collection Management and Analysis,

Data collection methods.

Data will be collected through an electronic Case Report From (eCRF). Inclusion and non-inclusion criteria, as well as attendance to each scheduled visit in the intervention group, will be prospectively entered into the eCRF. All other data, for maternal and neonatal outcomes, will be extracted from individual pregnancy records, in each of the participating centre, and collected into the electronic Case Report Form by clinical research assistant.

For the cost-effectiveness study, data for the first year of life will be extracted from the French Hospitalisation (PMSI) and Health Insurance (SNIIR-AM) databases, and analysed in Dijon University Health Centre

Data management.

The data will be managed by the Clinical Investigation Centre (CIC INSERM 1432) at Dijon University Hospital.

Statistical method

Descriptive analysis

Clinical and demographic characteristics of the patients will be presented, and the comparability of the two groups of patients regarding pregnancy risk factors will be assessed.

Primary outcome analysis

The primary criterion, as described previously, is binary. The principal analysis will be a proportion comparison using the Chi-squared test adjusted for the design effect, on an individual basis.

The cluster randomization ensuring a lower quality of the balance of the covariates, we will additionally study the following parameters, which potentially interfere with maternal or foetal

outcomes, using univariate logistic regression:

- type of centre (local / intermediate risk / high-risk maternity unit)
- proportion of deprived patients in the centre (three levels defined as <25th, 25th -75th and >75th percentile of the observed proportions in the different centres)
- age (<20, 20-35, >35 years old)
- parity (0, 1 or 2, more than 2)
- type of free healthcare (CMU-C/AME)

Interaction of these parameters and the effect of the intervention will be searched for using sub-group analyses.

A multivariable multilevel logistic regression adjusted for all the covariates with a p<0.20 will then be performed, taking into account the eventual interactions. A random effects term referring to clusters will be included in the model. The multivariate building process will use a stepwise approach. For each step, The Akaike information criterion (AIC) scores will be calculated to measure the relative goodness fit of the different models, where the lower the AIC, the better the fit. The model with the lowest AIC score will be upheld for the analyses.[27]

Secondary outcome analysis

1. Adverse outcomes in the child: same as the principal analysis, using this outcome.

2. Adverse outcomes in the mother: same as the principal analysis, using this outcome.

3. The number of prenatal consultations following the HAS standard care recommendations will be analysed using weighted means taking into account the cluster randomization.

An intermediate analysis will be performed after the first phase, but using a significance level of 0.0001 in order not to impair the study power.

Significance threshold

The results will be considered statistically significant if $p<0.05$.

Statistical software

The analyses will be performed using SAS software, latest version at the time of analysis. Statistician will be blinded for the study groups

Analysis of qualitative survey.

Raw data are analysed according to a thematic analysis method. From this progressive work of conceptualization and continuous comparison of the different situations, a theoretical system responding to our problems will be defined. A triangulation of data will be done as two sociologists will code the interview transcriptions. Nvivo software, which allows the creation of a code, and has been well validated for qualitative analyses will be used.[28] Qualitative data will be analysed during the data collection. The collection of data will be over as the concept saturation is done. Theoretical saturation will be assessed.[29] Practically, saturation is reached when no new data could add more information to meet the research objectives. So data are analysed by two researchers and the collection of data will be over as the two last interviews have not given any new information.

Statistical analysis of cost effectiveness.

A differential cost-effectiveness ratio associated with the intervention versus no intervention will be calculated by comparing the difference in average costs with the difference in average efficiencies. In order to test the robustness of the conclusions drawn, sensitivity analyses will be carried out on the parameters likely to have an influence on the results.

A nonparametric bootstrap analysis of the cost and efficiency differential observed between the two strategies will allow uncertainty to be taken into account and to estimate 95% confidence intervals for

the differential ratios of the baseline analysis.

Methods: Monitoring

Monitoring

As the study has been deemed non-interventional by the ethics committee, legally no formal monitoring is requested. Nonetheless the study will be monitored for quality and regulatory compliance. The monitoring will be supervised by the promoter (Dijon-Bourgogne University Hospital) in all of the participating centres. The frequency depends on inclusion rates, questions and pending issues from earlier audits: once or twice a year.

Harms

Steering and Data and Safety Monitoring Committees(DSMC):

The coordinating centre at CHU Dijon-Bourgogne, Centre d'Investigations Cliniques (CIC INSERM 1432), takes responsibility for all aspects of the study: ethical, regulatory, study conduction, data-management and publication strategy.

The steering committee is composed of the principal investigators of the first 10 centres, one representative from each perinatal care network involved in the study, a midwife, a social worker and a methodologist. A phone meeting is being held every four months. The role of the steering committee is to ensure that study is running according to study protocol and share solution to overcome difficulties in recruiting participants.

The data monitoring and safety committee (DSMC) is composed of two obstetricians specifically taking care of socioeconomically disadvantaged women, a methodologist, an ethics specialist, and a paediatrician. The DSMC will essentially review results of qualitative survey conducted during the first year, and follow observed versus expected, recruitment curves. If the qualitative survey were to suggest

that intervention stigmatize women, the scientific committee will have the right to stop the study. As management of women during their antenatal and post-natal period will be done according to French guidelines and will not be affected by the study, not harm other than potential stigmatisation is expected. No interim analysis has been planned, as it will have significantly impacted on sample size.

Auditing.

The study has been deemed non-interventional by the Ethics Committee, by law no formal auditing will be conducted.

Ethics and dissemination

Research Ethics approval.

Ethics approval was given by the Dijon ethics committee (CPP Est-1) on September 18th 2014, and the protocol was amended thereafter.

The study is funded by the French Ministry for Health in December 2014 (PREPS-14-0173) and promoted by Dijon Bourgogne University Hospital (France).

Authorization for holding the computerized databases was granted on March 21st 2016 by the National Committee for Informatics and Freedom (CNIL). This long delay was due to conflict between the reasoning of the CNIL, for which the preservation of private life is its top priority, and the French source of public funding, which needs to know precisely to whom public money, in this case the financial incentive, is being given.

It was registered in Clinicaltrials.gov with the identifier NCT02402855, on March 17th, 2015, at the French Research Agency with identifier 2014-A01319-38, and at the CNIL with request for authorization n°915385.

Protocol amendments.

The study is currently running according to the 5th amended version, June 30th 2016.

Consent or assent.

The study is non-interventional according to first approved version of the protocol, no formal consent is requested to be recruited.

A formal consent, from the women only, is requested for the collection of children data. (See information sheet in appendices)

Declaration of interests

Authors of the present paper have no competing interest to disclose.

Access to data:

Authors have no data to share at this stage. For reviewing purpose data will be shared with reviewers, and once the paper will have been published, data will be made available for scientific purpose.

Ancillary and post-trial care.

As the study does not affect usual care of women, no post-trial care has been scheduled. No ancillary studies have been planned so-far

Dissemination policy.

A manuscript with the results of the primary study will be published in a peer-reviewed journal. Separate manuscripts will be written on each of the secondary aims, and these will also be submitted for publication in peer-reviewed journals.

Presentation of the results will be done at scientific meetings, and specific communication will be organised to target health professionals, policy decision makers, regulatory bodies, and patients.

Recruitment is on-going; the first patients were recruited on June 4th 2016 in the control group and on June 10th 2016 in the intervention group.

Discussion.

This will be the first study to provide rigorous evidence regarding the effectiveness of financial incentives, to improve the use of prenatal care, on perinatal outcomes for the mother and the foetus. A recent Cochrane meta-analysis,[21] emphasized the need for such an assessment, and it is of particular interest to note that no such studies have been carried in Europe so far.

The conditional cash-transfer is not supposed to replace any other public health policies aimed to promote appropriate prenatal care but it may help to overcome some of the barriers that stand in the way of adequate follow-up. Most of the studies have been conducted in low-income countries, where, besides many other factors, the structure of the health care system and health care facilities are very different from those in developed Countries.

For example, in 2005, the Indian Government implemented the Janani Suraksha Yojana program, which incentivizes poor women to give birth in a health facility by providing them with a cash transfer upon discharge. There was, however, no formal assessment of the efficacy. Whereas this program was associated with a very significant increase in the rate of delivery in health care facilities (from 39% to 74%), a recent survey suggested that beyond the cash incentive, the shift in the social norm and the women's own perception played a major role in this effect.[30] Interestingly, this program was shown to be associated with a reduction in neonatal and perinatal deaths.[31]

Financial incentive programs to promote smoking cessation during pregnancy have been assessed and have recently been reported to be associated with a reduced odds of low-birth weight.[32]

If our intervention proves to be effective, its implementation may have to overcome several difficulties, including tailoring the intervention to women most likely to respond, increasing acceptability of the

concept among public bodies and health professionals, and proving the intervention to be cost effective. It has been suggested that for some interventions, efforts have to be made to increase acceptability, even when they have been proven to be effective.[33] All of these aspects will be covered by our research program.

The investigators have no conflicts of interest to declare.

***NAITRE study group:**

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Contributorship statement:

Study design: Bardou M, Crépon C, Bertaux A-C, Godard-Marceaux A, Duflo E, and Le Ray I..

Obtaining funding and drafting publication: Bardou M,

Reviewing and amendment of the protocol, reviewing of the paper: Eckman-Lacroix A, Thellier E, Falchier F, Deruelle P, Doret M, Carcopino-Tusoli X, Schmitz T, Barjat T, Morin M, Perrotin F, Hatem G, Deneux-Tharaux C, Fournel I, Laforet L, Meunier-Beillard N

Authorship eligibility guidelines and any intended use of professional writers. Marc Bardou will be first author of the main publication of study results, he will be last author of affiliated papers, if any, such as results of the qualitative and the cost effectiveness surveys. Godart-Marceau A, will be first author of the qualitative survey and Bertaux AC of the cost effectiveness study. Bardou, M will signed as last author. One investigator will be listed as authors in each of the participating centre, with the investigator of the best recruiting centre (based on the number of participant recruited prorated on the time spent by the centre into the study and the number of pregnancies followed-up during that time). There is no intended use of professional writer.

Funding:

The study has been funded by the Ministère de la Santé, Ditection Générale de l'Ofrre de Soins (DGOS) (Grant number PREPS-14-0173).

Sponsor: CHU Dijon-Bourgogne, Délégation à la Recherche Clinique et à l'Innovation.

Sponsor Contact Person: Catherine Renaud, tel + 33 380 29 31 53; catherine.renaud@chu-dijon.fr

Neither funder nor sponsor had any role in the study design, writing of this report, or the decision to submit the report for publication.

Supplementary files.

Annex 1 and 2. Information and consent sheets from for the intervention and control groups respectively.

Annex 3. Interview grid for the qualitative survey

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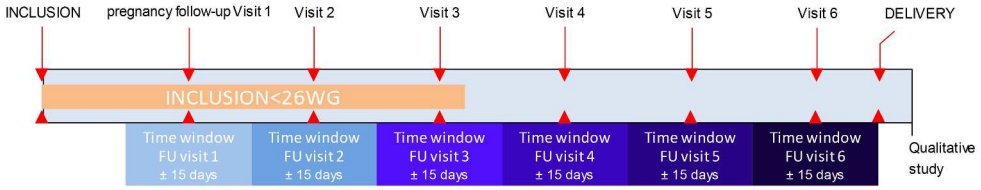
Figure legends.

Figure 1. Scheduled prenatal care visit and time window for financial incentives. If a women shows up for a scheduled more than 2 weeks after her standard pre planned agenda, she will receive the incentive for the next visit. It means that she won't attend a scheduled visit without receiving an incentive (with the limit of no more than one incentivised visit per month), but she may receive less incentive that the maximum she could have had access to.

Figure 2. Overall management of women, according to their group of allocation. CRA = Clinical Research Assistant.



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319x61mm (300 x 300 DPI)

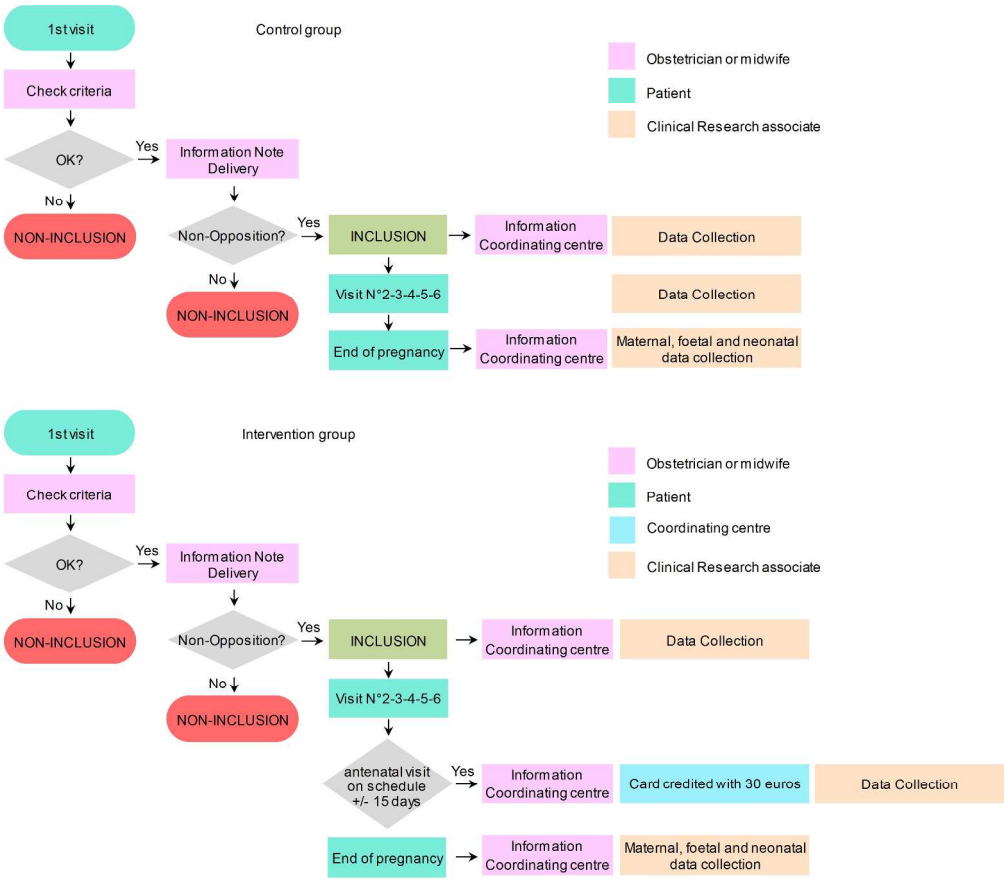

Figure 2. Overall management of women, according to their group of allocation. CRA = Clinical Research Assistant.

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Référence Etude / Study Reference : NAITRE
Note d'information / Information Sheet : Version n° 04 (30/06/2016)

Information sheet

Evaluation of the impact of financial support on the medical follow-up and pregnancy outcomes in pregnant women who benefit from CMU, CMU-C or AME

Registration N°: 2014-A01319-38

Organizer of the research project: ***Dijon University Hospital***

Person directing and supervising the research: ***Professor Marc BARDOU**, medical coordinator of the Clinical Investigation Centre 1432, plurithematic module*

Madam,

Your doctor has suggested you take part in research aiming to evaluate care currently provided by Dijon University Hospital. Before making your decision, it is important for you to read the following pages attentively. They will provide necessary information concerning the different aspects of this research. Feel free to ask any questions you wish.

Your participation in this research is entirely voluntary and you have the right to refuse to take part. In such a case, you will continue to benefit from the best medical care possible, in accordance with current knowledge.

Why this research?

The frequency of complications in pregnancy, such as the prematurity or low birth weight, is almost 50% higher in women who depend on social support than in those whose revenue comes from their work.

These high-risk pregnancies should be particularly well followed so as to detect and treat complications early. Universal Medical Cover (CMU), CMU-C (complementary) and State Medical Aid (AME) ensure that people who meet specific French government criteria have access to health care. However, a third of those entitled to CMU refuse care for financial reasons and ¼ of female patients who rely on welfare support have fewer than 7 consultations during their pregnancy. The recommendations of the health authorities (Haute Autorité of Santé) on the minimal follow-up are thus not respected.

What is the aim of this research?

To determine whether financial support provided on condition that patients respect at least the minimum recommendations of the Health Authorities can reduce the rates of pregnancy complications, for the mother and her child, for pregnant women who benefit from CMU, CMU-C or AME (state of health during their pregnancy, and that of the baby at birth).

How is the research organized?

You have come to the hospital to declare your pregnancy. You will have a medical examination with regard to your pregnancy. The results of this examination will be given to you.

The medical team will propose medical follow-up for your pregnancy in accordance with Health Authority recommendations, which means attending at least 7 follow-up consultations during your pregnancy.

You will be given € 30 (thirty euros) for each of the scheduled follow-up visits (**6 maximum**) you attend, if they are done according to your doctor's recommendations. This money will be given in the form of a payment card at the next consultation. The card will be credited after each of the **follow-up consultations** scheduled by your doctor or the midwife who is following your pregnancy **you attend** (**other than emergency consultations, other than follow-up consultations for illness**).

You will have no other additional medical examinations (consultations, echography, blood tests) because of the research.

Emergency consultations will not give rise to financial compensation.

If the state of your pregnancy requires specific management involving **more frequent consultations, no additional financial compensation will be provided**.

What do you have to do?

If you accept, we will collect in a strictly anonymous manner the information in your medical record concerning your medical history, your ethnic origin, the follow-up of your pregnancy and the delivery, your state of health and that of your child.

What are the possible drawbacks?

Your participation will have no impact on the medical care provided by the medical team.

What are your rights?

This study has been approved by the ethics committee "Comité de Protection des Personnes (CPP) Est I", le 28/10/2014.

This study will be carried out in accordance with the law on medical secrecy "informatique et liberté" (*la loi du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés* modifiée par la *loi du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements des données à caractère personnel*) (the law of 6 January 1978 relative to computerized information, to files and liberty modified by the law of 6 August 2004 relative to the protection of persons with regard to the processing of personal data).
You have the **right to see and to rectify** your computerized records and to **oppose** the transmission of your data used in the context of this study. These rights can be exercised by contacting the coordinating centre for the study (at the address and telephone number below).

Your medical and personal data will be processed by computer to analyse the results. The processing will be anonymous and confidential as your data will be identified only by your initials associated with a code number. The data will be transmitted to the research organizer.

At any time during the study, you can contact the investigating doctor to obtain any additional information you may need about the study, about your participation or about your personal health data.

If you wish, you can be informed about the overall results of the research at the end of the study by the coordinating centre.

The results of this study may be used for communications and/or published in scientific journals. Your identity will not appear in these.

Your participation is voluntary and of your own free will

Your refusal to take part will have no impact on the type and the quality of your care, or on your relationship with the medical team.

If you accept to take part, you can leave the study at any time without giving a reason. Leaving the study will have no impact on the quality of your care.

The information collected before you leave the study will be used unless you do not wish so. In this case you must inform the investigating doctor.

Thank you for your cooperation.
If you agree to take part in this study,
please give your verbal agreement.

Investigating Centre / Centre Investigateur :

Logo of the centre/ Etiquette centre :
Identity of the Principal Investigator/ Identité Investigateur Principal :
Address / Adresse :
Telephone/ Téléphone :

Coordinating Centre / Centre coordonateur :

DIJON CHU,
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BP 77908, 21079 DIJON CEDEX;
☎: 03.80.29.57.53; email: cic-p@chu-dijon.fr

Exemplaire à remettre à la patiente

Consent form for the collection and processing of data for the « NAITRE » study.	**Formulaire de consentement au recueil et au traitement des données dans le cadre de l'étude NAITRE**
Evaluation of the impact of financial support on the medical follow-up and pregnancy outcomes in pregnant women who benefit from CMU, CMU-C or AME	*Evaluation de l'impact d'une compensation économique sur le suivi médical et le devenir de la grossesse chez des femmes enceintes bénéficiaires de la CMU, de la CMU-C ou de l'AME*
Registration N°: 2014-A01319-38 *Organizer of the research project:Dijon University Hospital* *Person directing and supervising the research: Professor Marc BARDOU, medical coordinator of the Clinical Investigation Centre 1432, plurithematic module*	*N° d'enregistrement : 2014-A01319-38* *Gestionnaire du projet de recherche : Centre Hospitalier Universitaire de Dijon* *Personne qui dirige et surveille la recherche : Professeur Marc BARDOU, coordonnateur médical du centre d'investigation clinique 1432, module plurithématique*
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Anglais / INTERV

EXEMPLAIRE A CONSERVER SUR SITE

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Anglais / INTERV

Etude NAITRE - Auto-questionnaire à compléter par les patientes au moment de leur inclusion

Identification patiente (n° de centre – n° d'inclusion dans le centre) : |__||__| - |__||__||__||__|

Madame,

Vous avez accepté de participer à l'étude NAITRE sur le devenir de la grossesse chez des femmes bénéficiaires de la CMU, de la CMU-C ou l'AME. Nous vous remercions de bien vouloir répondre aux questions suivantes.

Rencontrez-vous parfois un travailleur social ?	☐ OUI / ☐ NON
Bénéficiez-vous d'une assurance maladie complémentaire ?	☐ OUI / ☐ NON
Vivez-vous en couple ?	☐ OUI / ☐ NON
Êtes-vous propriétaire de votre logement ?	☐ OUI / ☐ NON
Y-a-t-il des périodes dans le mois où vous rencontrez de réelles difficultés financières à faire face à vos besoins (alimentation, loyer, EDF…) ?	☐ OUI / ☐ NON
Vous est-il arrivé de faire du sport au cours des 12 derniers mois ?	☐ OUI / ☐ NON
Êtes-vous allée au spectacle au cours des 12 derniers mois ?	☐ OUI / ☐ NON
Êtes-vous partie en vacances au cours des 12 derniers mois ?	☐ OUI / ☐ NON
Au cours des 6 derniers mois, avez-vous eu des contacts avec des membres de votre famille autres que vos parents ou vos enfants ?	☐ OUI / ☐ NON
En cas de difficultés, y a-t-il dans votre entourage des personnes sur qui vous puissiez compter pour vous héberger quelques jours en cas de besoin ?	☐ OUI / ☐ NON
En cas de difficultés, y a-t-il dans votre entourage des personnes sur qui vous puissiez compter pour vous apporter une aide matérielle ?	☐ OUI / ☐ NON

Quelle est votre durée quotidienne de transport pour vous rendre à votre travail **(temps aller-retour domicile-travail) ?**	☐ sans activité professionnelle ou ☐ inférieure ou égale à 30 min (≤30 min) ☐ entre 30 min et 60 min (> 30 min et ≤ 60 min) ☐ entre 1 h et 2h (> 1h et ≤ 2h) ☐ supérieure à 2 h (> 2h)

Quel mode de transport avez-vous utilisé pour vous rendre à cette consultation de suivi de grossesse ?	☐ Véhicule personnel ou véhiculée par un proche (famille, ami) ☐ Transports en commun (bus, métro, train, …) ☐ Autre moyen de transport → précisez : _ _ _ _ _ _ _ _ _ _ _ _

Information sheet

Medical follow-up and pregnancy outcomes in pregnant women who benefit from CMU, CMU-C or AME

Registration N°: 2014-A01319-38

Organizer of the research project: ***Dijon University Hospital***

Person directing and supervising the research: ***Professor Marc BARDOU**, medical coordinator of the Clinical Investigation Centre 1432, plurithematic module*

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Your doctor has suggested you take part in research aiming to evaluate care currently provided by Dijon University Hospital. Before making your decision, it is important for you to read the following pages attentively. They will provide necessary information concerning the different aspects of this research. Feel free to ask any questions you wish.

Your participation in this research is entirely voluntary and you have the right to refuse to take part. In such a case, you will continue to benefit from the best medical care possible, in accordance with current knowledge.

Why this research?

Universal Medical Cover (CMU), CMU-C (complementary)) and State Medical Aid (AME) ensure that people who meet specific French government criteria have access to health care. However, certain beneficiaries may avoid seeking care, especially during pregnancy. The same is true for persons covered by the National Health Insurance Scheme but without private mutual health insurance. We wish to describe these situations, as well as their consequences for the mother and child.

What is the aim of this research?

To collect information concerning pregnant women who benefit from CMU, CMU-C or AME (state of health during their pregnancy, and that of the baby at birth).

How is the research organized?

You have come to the hospital to declare your pregnancy. You will have a medical examination with regard to your pregnancy. The results of this examination will be given to you.
The medical team will propose medical follow-up for your pregnancy in accordance with Health Authority recommendations, which means attending at least 7 follow-up consultations during your pregnancy.
Your medical follow-up will follow the normal process as planned by the doctor or midwife will follow you, with no involvement of the research team. If you accept, we will collect in a strictly confidential and anonymous manner the information from your medical record concerning your medical history, your ethnic origin, the follow up of your pregnancy and your delivery, your state of health and that of your baby.

You will have no other additional medical examinations (consultations, echography, blood tests) because of the research.

What are your rights?

This study has been approved by the ethics committee "Comité de Protection des Personnes (CPP) Est I", le 28/10/2014.

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If you wish, you can be informed about the overall results of the research at the end of the study by the coordinating centre.

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Référence Etude / Study Reference : NAITRE
Formulaire de consentement au recueil et au traitement des données / Version n° 01 (28/12/2015)
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Madame,

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Rencontrez-vous parfois un travailleur social ?	☐ OUI / ☐ NON
Bénéficiez-vous d'une assurance maladie complémentaire ?	☐ OUI / ☐ NON
Vivez-vous en couple ?	☐ OUI / ☐ NON
Êtes-vous propriétaire de votre logement ?	☐ OUI / ☐ NON
Y-a-t-il des périodes dans le mois où vous rencontrez de réelles difficultés financières à faire face à vos besoins (alimentation, loyer, EDF…) ?	☐ OUI / ☐ NON
Vous est-il arrivé de faire du sport au cours des 12 derniers mois ?	☐ OUI / ☐ NON
Êtes-vous allée au spectacle au cours des 12 derniers mois ?	☐ OUI / ☐ NON
Êtes-vous partie en vacances au cours des 12 derniers mois ?	☐ OUI / ☐ NON
Au cours des 6 derniers mois, avez-vous eu des contacts avec des membres de votre famille autres que vos parents ou vos enfants ?	☐ OUI / ☐ NON
En cas de difficultés, y a-t-il dans votre entourage des personnes sur qui vous puissiez compter pour vous héberger quelques jours en cas de besoin ?	☐ OUI / ☐ NON
En cas de difficultés, y a-t-il dans votre entourage des personnes sur qui vous puissiez compter pour vous apporter une aide matérielle ?	☐ OUI / ☐ NON

Quelle est votre durée quotidienne de transport pour vous rendre à votre travail **(temps aller-retour domicile-travail) ?**	☐ sans activité professionnelle ou ☐ inférieure ou égale à 30 min (≤30 min) ☐ entre 30 min et 60 min (> 30 min et ≤ 60 min) ☐ entre 1 h et 2h (> 1h et ≤ 2h) ☐ supérieure à 2 h (> 2h)

Quel mode de transport avez-vous utilisé pour vous rendre à cette consultation de suivi de grossesse ?	☐ Véhicule personnel ou véhiculée par un proche (famille, ami) ☐ Transports en commun (bus, métro, train, …) ☐ Autre moyen de transport → précisez : _ _ _ _ _ _ _ _ _ _ _ _

Ouverture de l'entretien

Grille d'entretien

Moment de l'entretien : lors de la visite post natale (6 semaines après l'accouchement)

Lieu de l'entretien : Domicile ou centre de consultation

Présentation du chercheur

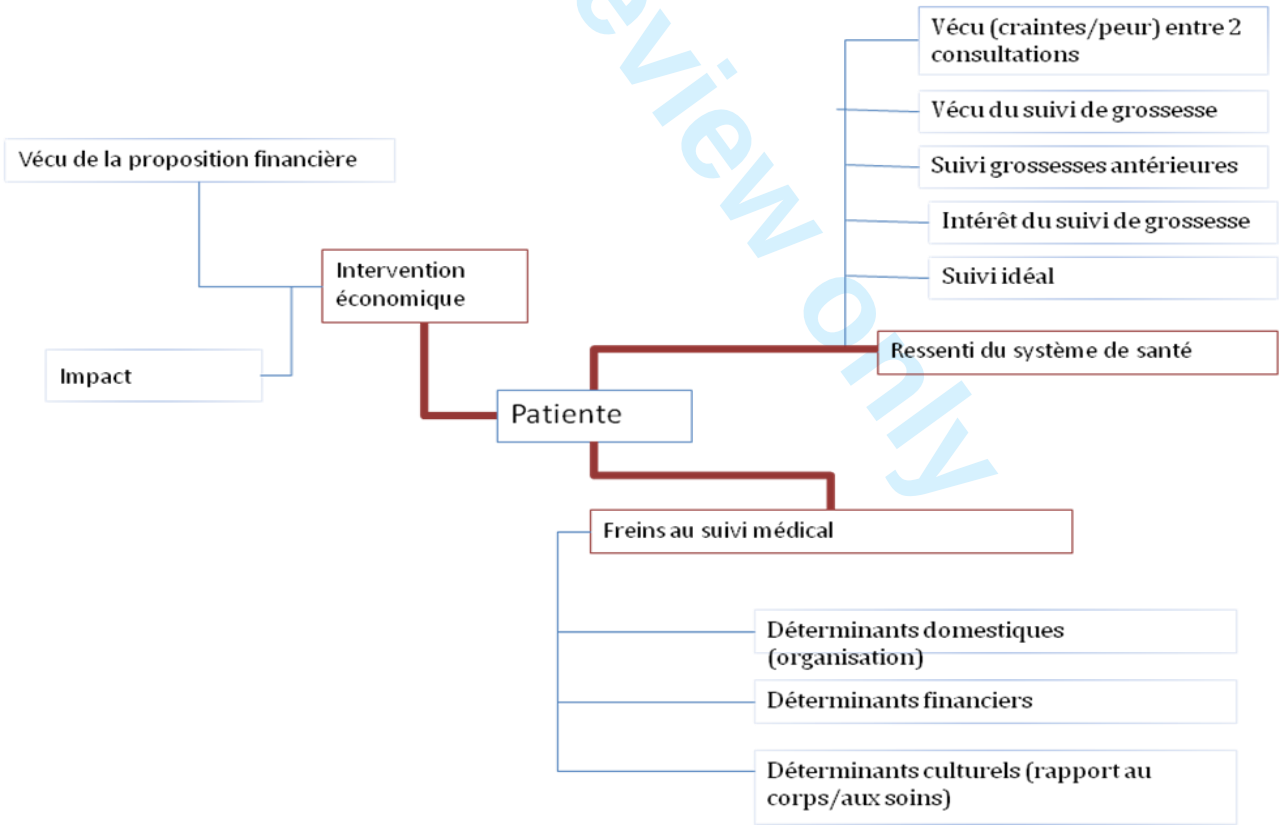
Rappeler leur inclusion dans une étude.

Rappeler qu'on est chercheur.

Objet de l'entretien : vécu de la participation dans cette étude.

Schéma de l'entretien

Selon les informations dont nous disposons en amont**, l'entretien pourrait se terminer** par quelques questions sur l'histoire de vie des femmes rencontrées.



Pouvez-vous me raconter comment s'est déroulée votre grossesse ?
Renoncement aux soins Quelles ont été les difficultés que vous avez rencontrées pour assister à ces consultations ?
Ressenti du suivi médical Le ministère préconise 7 visites médicales et 3 échographies, que pensez-vous de ces préconisations ?
Impact de l'intervention A votre avis, qu'est-ce qui vous aurait aidé à assister au nombre de consultations recommandé ? ➔ Pour les femmes appartenant au bras hors intervention : Si une compensation financière vous était proposée pour chaque rendez-vous effectué, qu'en penseriez-vous ? Quelle utilisation en auriez-vous fait ? Quelle somme pourrait- être proposée ? ➔ Pour les femmes appartenant au bras invention : Que pensez-vous de la proposition faite par le médecin de vous remettre une carte créditée pour chaque visite médicale effectuée ? Quelle utilisation en avez-vous fait ? Que pensez-vous de la somme qui vous été donné ? (beaucoup, pas assez ?)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ☑
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ☑
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier ☑
Funding	4	Sources and types of financial, material, and other support ☑
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor ☑
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities ☑
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) ☑
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ☑
	6b	Explanation for choice of comparators ☑
Objectives	7	Specific objectives or hypotheses ☑
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) ☑

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained ☑
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ☑
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ☑
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) ☑
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ☑
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial ☑
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended ☑
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) ☑
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations ☑
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ☑

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions ☑

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned ☑
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions ☑
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how ☑
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial ☑
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol ☑
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols ☑
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol ☑
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol ☑
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) ☑
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) ☑
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed ☑

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ☑
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ☑
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ☑
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ☑
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ☑
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ☑
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable ☑
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ☑
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ☑
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ☑
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation ☑
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions ☑
	31b	Authorship eligibility guidelines and any intended use of professional writers ☑
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **NA**

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ☑
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **NA**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

The NAITRE study - Impact of conditional cash transfer on poor pregnancy outcomes in underprivileged women: protocol for a nationwide pragmatic cluster-randomized superiority clinical trial in France.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017321.R2
Article Type:	Protocol
Date Submitted by the Author:	15-Sep-2017

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Health services research, Evidence based practice, Health policy
Keywords:	Clinical governance < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS

The NAITRE study - Impact of conditional cash transfer on poor pregnancy outcomes in underprivileged women: protocol for a nationwide pragmatic cluster-randomized superiority clinical trial in France.

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Abstract

Introduction. Prenatal care is recommended during pregnancy to improve neonatal and maternal outcomes. Women of lower socio-economic status (SES) are less compliant to recommended prenatal care and suffer a higher risk of adverse perinatal outcomes. Several attempts to encourage optimal pregnancy follow-up have shown controversial results, particularly in high-income countries. Few studies have assessed financial incentives to encourage prenatal care, and none reported materno-foetal events as the primary outcome. Our study aims to determine whether financial incentives could improve pregnancy outcomes in women with low SES in a high-income country.

Methods and analysis. This pragmatic cluster-randomized clinical trial includes pregnant women with the following criteria: i) age above 18 years, ii) first pregnancy visit before 26 weeks of gestation, iii) belonging to a socioeconomically disadvantaged group. The intervention consists in offering financial incentives conditional on attending scheduled pregnancy follow-up consultations. Clusters are 2-month periods with random turnover across centres. A composite outcome of maternal and neonatal morbidity and mortality is the primary endpoint. Secondary endpoints include maternal or neonatal outcomes assessed separately, qualitative assessment of the perception of the intervention, and cost-effectiveness analysis for which children will be followed to the end of their first year through the French health insurance database. The study started in June 2016, and based on an expected decrease in the primary endpoint from 18% to 14% in the intervention group, we plan to include 2000 women in each group.

Ethics and dissemination. Ethics approval was first gained on September 28th 2014. An independent data security and monitoring committee has been established. Results of the main trial and each of the secondary analyses will be submitted for publication in a peer-reviewed journal.

Trial Registration number. NCT02402855 (March 17 2015) (Protocol version 5, June 30, 2016)

Strengths and limitations of this study

- Inadequate prenatal care has been associated with poor pregnancy outcomes, and in high-income countries, socioeconomically disadvantaged women have increased rates of both unattended pregnancy follow-up visits and pregnancy-related adverse outcomes. Among interventions that aim to promote adequate prenatal care, financial incentives have the potential to overcome some of the barriers, but data on the reality and the magnitude of such an effect on pregnancy outcomes are sparse.
- A cluster randomized clinical trial, using a Zelen design, will run in about 40 public maternity units all over France, with the aim to include a total of 4000 women. The intervention group will receive a €30 incentive for each scheduled prenatal visit they have attended. The control group will be followed according to the national recommendations and local practices.
- The main outcome is a composite of maternal and neonatal adverse outcomes. Secondary outcomes will include qualitative assessments and the cost-effectiveness of intervention.
- The definition of the low socioeconomic group relies on the type of health-care insurance alone, no individual assessment will be conducted.
- Follow-up of children until their first birthday will only rely on electronic data from the French Health Insurance database

INTRODUCTION

Background and rationale. Prenatal care, i.e. the medical and nursing care recommended during pregnancy, aims to prevent, if possible, any potential problems or to detect them early to organise appropriate management. A number of studies have demonstrated a relationship between fewer prenatal visits and poorer pregnancy outcomes. A large retrospective cohort in the United States demonstrated that women with inadequate prenatal care (defined as attending fewer than 50% of recommended visits) had an increased risk of preterm birth (OR 2.0, 95% CI 1.9-2.0), low birth-weight (OR 1.7, 95%CI 1.6-1.7), and infant mortality (OR 1.5, 95%CI 1.3-1.7) compared to women who received adequate prenatal follow-up.[1] This association is even stronger in European cohort studies, even after adjusting for confounding factors.[23 4]

As the provision of prenatal care to pregnant women appears to be an effective way to improve perinatal outcomes, many countries have implemented specific recommendations for this care, with various expectations in different countries, the minimum being eight antenatal contacts, as recommended by the WHO.[5]

Appropriate pregnancy follow-up is based on early initial access to a health professional and adequate compliance with the scheduled follow-up visits. It has been suggested that initial access is influenced by late recognition of the pregnancy and subsequent denial or acceptance whereas follow-up depends on a strategy of weighing up and balancing out the perceived gains and losses. Personal resources in terms of time, money and social support as well as the services available are all taken into account.[6]

Perinatal outcomes in socioeconomically disadvantaged populations have been shown to be worse than those in the rest of the population, in terms of perinatal death,[7,8] prematurity,[9 10] congenital anomalies, and low birth weight.[11]. [10108]

[12 13]Access to prenatal care is insufficient in this at-risk population. This has been demonstrated in countries where access to care is not equal, such as the United States, as well as in countries such as Belgium or France, where free healthcare is provided for socially disadvantaged populations.[14 15] In

France, for example, the preliminary results of the preCARE cohort, which analysed data of about 10000 women, suggested that women covered with insurance for low-income people (CMU for Couverture Maladie Universelle or Universal Medical Coverage) and insurance for illegal immigrants (AME for Aide Médicale d'Etat or State Medical Assistance) have respectively a 50% and 80% increased risk of severe maternal morbidity (Relative Risk of 1.5; 95%CI: 0.95-2.3 and 1.8; 95% CI 1.1-3.1, for CMU and AME women, respectively)[4].

In addition, adequate prenatal care has been shown to be cost-effective. This effect is largely due to the extremely high cost of care for preterm and low birth-weight infants, with costs standing at over US$ 100,000 for extreme prematurity, between US$ 40,000 and US$ 100,000 for early prematurity, between US$ 10,000 and US$ 30,000 for moderate prematurity and below US$ 4,500 for late prematurity.[16]

Several interventions to improve pregnancy follow-up have been assessed, and most of the recent literature on this topic has come from low- and middle-income countries. In a systematic review published in 2016, Lassi and colleagues[17] assessed human resources for health (HRH) and showed that HRH interventions could contribute positively to the health worker's performance and thus improve maternal outcomes. The meta-analysis published in 2015 by the same authors suggested that community-based intervention packages could lead to a significant reduction in neonatal mortality (RR 0.75, 95% CI 0.67-0.83), and a possible effect on maternal mortality (RR 0.80; 95%CI 0.64-1.00).[18]

In the few studies conducted in high-income countries recently, several reinforcement interventions have been tested. A study conducted in the US among primiparous African-American women assessed four levels of incremental interventions, which combined financial support with enhanced post-delivery follow-up.[19] None of these interventions proved to be effective, even as a numerical trend, in reducing premature delivery or the proportion of SGA infants.

More recently, a study conducted in Ireland, among women from a disadvantaged community in Dublin, showed that a home-visit program had no impact on any of the neonatal outcomes.[20] In

contrast[20], a meta-analysis published in 2016 by Sandal J and colleagues suggested that women who received midwife-led continuity models of care were less likely to experience poor pregnancy outcomes than women who received other models of care.[21]

Some studies have suggested that the use of incentives may improve prenatal care, and neonatal outcomes. A retrospective cohort study in Canada demonstrated that low-income pregnant women who participated in a prenatal support program beginning early in pregnancy (before 21 weeks of gestation) had significantly decreased rates of low birthweight (LBW) infants compared to women who enrolled later in pregnancy (after 30 weeks of gestation) (risk ratio (RR) 0.47, 95% CI 0.22-0.98).[22]

A Cochrane review on this topic published in 2015[23] was only able to show that pregnant women receiving incentives were more likely to obtain adequate quality prenatal care (mean difference 5.84, 95%CI 1.88-9.80) as none of the included trials reported on preterm birth, small for gestational age and perinatal deaths. This Cochrane review concluded that data from randomized trials, powered to show results on maternal and neonatal outcome, are urgently needed to inform public health authorities. Although it has been suggested that incentive programs are effective, for example, for smoking cessation during pregnancy,[24] this approach remains highly controversial.[25]

This paper describes the protocol of an adequately powered cluster-RCT to explore the effectiveness on perinatal outcomes of financial incentives linked to the use of prenatal care and targeting socioeconomically disadvantaged women.

Objectives:

Primary objectives

The primary objective is to assess the superiority of a conditional cash transfer program in addition to the best standard of care compared with the best standard of care alone among socioeconomically disadvantaged women. The best standard of care is based on the guidelines defined by French health authorities (HAS), and superiority will be assessed in terms of maternal-foetal outcomes.

Secondary objectives

1. To determine whether a conditional cash transfer program can improve neonatal outcomes
2. To determine whether a conditional cash transfer program can improve maternal pregnancy outcomes.
3. To assess through a qualitative approach, among women of the incentive program group, their acceptance of the program, and whether it has a significant impact on their adherence to prenatal care
4. To assess, among women from both groups, determinants of inadequate prenatal care
5. To assess the cost-effectiveness and budget impact of the conditional cash transfer program compared with the best standard of care without the conditional cash transfer

Trial design.

The NAITRE study is a pragmatic multi-centre, open-label cluster-randomized trial using a parallel arm design.

Methods: Participants, interventions, outcomes

Study setting

During year one of the study, June 2016 to June 2017, 10 centres, all tertiary obstetric departments, included women. These centres are located throughout France. Starting in June 2017 the study will be extended to about 30 additional primary to tertiary Obstetric departments, assuming the qualitative study shows no negative feeling of the women (see specific section below).

The cluster randomization procedure was chosen in order to allow a Zelen design,[26] i.e. women being randomized before they consent to participate, and only receiving information for the group they will be allocated to. This is of particular relevance as when patients do not receive their preferred treatment

in randomized trials there may be difficulties with patient recruitment and scientific problems with bias. Centres, and not women, are being randomized. To account for heterogeneity among centres and the relatively small number of centres, about 40, clusters are 2-month periods with random turnover across centres, meaning that each centre will contribute both to the intervention and the control groups. Patient enrolment started in June 2016 and is expected to end in December 2019.

The study was approved by a central ethics committee (Comité de Protection des Personnes Est-1), by the French Medicines Agency, and data collection and recording was approved by the CNIL (Commission Informatique et liberté).

Figure 1 summarizes the design of the trial and each aspect of the trial is described in detail below.

Eligibility criteria:

The study includes pregnant women: 1) above the age of 18, 2) with their first pregnancy visit in one of the participating centres before the end of the 26th week of amenorrhea, 3) with social insurance for low-income people (CMU for Universal Medical Coverage) or illegal immigrant status (AME for Aide Médicale d'Etat or State Medical Insurance)

The only non-inclusion criteria are: 1) women not able to understand the study, 2) women under legal supervision. There are no other restrictions to the inclusion criteria as the study has a pragmatic concept.

Interventions.

Control group:

Women in the control group receive prenatal care according to the standard practice, as set out in national guidelines. Women's personal medical history and pregnancy medical data are collected up to one month post discharge after delivery whereas data for their child will be collected up to their first birthday.

Intervention group

Women in the intervention group are given a payment card on their first visit, the inclusion visit. The card will be credited with €30 after each scheduled prenatal visit, with a maximum of one €30 incentive per month. Cash transfer starts at the first scheduled visit after the inclusion visit.

No additional incentives will be provided if more visits are deemed necessary because of a specific pregnancy follow-up program, or unplanned visits to the emergency department. Inclusion using the eCRF automatically generates the scheduled prenatal visits program according to the national guidelines. *Figure one* shows the agenda for prenatal visits with time windows for incentives.

Outcomes

Primary outcome

The primary endpoint is a global composite endpoint of perinatal morbidity and mortality, defined as the occurrence of at least one complication of pregnancy, whether maternal, foetal or neonatal.

- For infants: perinatal death, premature birth (before 37 weeks of amenorrhea), intrauterine growth restriction (estimated weight < the 10th percentile for gestational age and abdominal circumference below the 2.5th percentile), low birth weight (<2500g at term), early neonatal encephalopathy (asphyxia at birth and cerebral anomalies of neonatal or perinatal origin (anoxic or ischemic encephalopathy, periventricular leukomalacia or intraventricular haemorrhage), lesion of the brachial plexus (clinical diagnosis), probable or certain maternal-foetal infection (clinical and biological diagnosis). Birth of a child with a congenital abnormality is considered a failure if it results from a lack of prenatal diagnosis, but a success if it results from parental choice. Therapeutic interruptions of pregnancy for congenital malformation diagnosed during pregnancy are likewise considered part of the optimal follow-up and are counted as successes.
- For the mother: maternal death, phlebitis, pulmonary embolism (diagnosed by Doppler

ultrasound of the lower limbs and/or spiral scan and/or pulmonary scintigraphy), pre-eclampsia or eclampsia, postpartum haemorrhage requiring transfusion, conservative surgery or embolization of uterine arteries or hysterectomy, postpartum endometritis (clinical diagnosis), 3rd or 4th degree perineal lesion with anal sphincter injury.

Perinatal outcomes will be assessed at hospital discharge of both the mother and the infant (last discharged).

Secondary outcomes

1. Adverse perinatal outcome in the child, as previously defined.
2. Adverse perinatal outcome in the mother, as previously defined.
3. Number of prenatal consultations following the French standard care recommendations. All outpatient visits, including those prospectively scheduled by the study protocol, will be retrieved using the French Health Insurance database (SNIIR-AM)
4. Qualitative assessment of barriers to adequate prenatal follow-up and the perception of the intervention by some of the participating women and health professionals.
5. Differential cost-effectiveness ratio associated with financial incentive versus no compensation and expressed in terms of cost per complication avoided.
6. Overall budget impact

Participant timelines.

Women will be followed according to the official antenatal care program and to requests from their obstetrician. No additional visits or tests of any type will be requested because of their participation in the trial. Data will be recorded from inclusion to discharge from the maternity ward.

New-borns will be followed up to discharge from hospital.

For the cost-effectiveness study, data on health resources utilisation, i.e. outpatient clinics, blood or imaging tests performed and medication purchased will be collected through the national health insurance database, up to the first year of age for the children.

Figure 2 shows the overall management of women included in the study according to the randomisation group.

Sample Size

According to the 2010 French perinatal survey, the estimated prevalence of adverse pregnancy outcomes, according to our primary outcome definition is estimated at 12% in the general population and 18% in socioeconomically disadvantaged women.[27] The hypothesis supporting our sample size calculation is that the financial incentive, by increasing adherence to prenatal care, can reduce this difference by two-thirds, thus resulting in a rate of complicated pregnancies in the intervention group of 14%. To ensure a power of 80% and a significance level of 0.05, 1,314 women per group are needed.

In order to obtain accurate data, the frequency of randomization was set at every two months. According to the randomisation procedure, we will have 420 clusters (2-month periods over 3 years for the 10 participating maternity departments of the first phase and over 2 years in the up to 30 additional centres included in second phase) and about 8 women per cluster.

We hypothesized an intra-cluster correlation coefficient (ICC) of 0.01, meaning that 1,526 women are necessary.[28] Allowing for 20% attrition, 1,900 women per group are needed, and we set the sample size at 2,000 per group. An ICC of 0.01 was selected because the trial assesses an intervention aimed directly at the patient and an outcome measurement for which the variance between practices is low compared with the variability between patients within a practice.

Recruitment

All eligible women registering for maternity care at the trial sites during the study period will be invited to participate in the study. The list of the participating centres can be found on ClinicalTrials.gov (NCT02402855).

Information sheet and consent form for the intervention group (annex 1) and the control group (annex 2) are available in 18 languages. The self-administered deprivation questionnaire embedded in both forms is available in French only.

Cost-effectiveness analysis

Study design

A cost-effectiveness analysis comparing the financial incentive strategy associated with prenatal care of socio-economically disadvantaged women versus no financial incentive will be carried out. The reference strategy is standard prenatal care in the absence of financial incentives.

This analysis will be conducted from a societal perspective in such a way as to favour a sufficiently broad perspective to take into account all stakeholders involved in the intervention.

Outcomes

Efficacy is a composite criterion that includes complications of the child during his/her first year of life (such as perinatal death, prematurity or neurological impairment) and maternal adverse events (including post-partum haemorrhage, endometritis). Direct costs will be considered from a societal perspective. The effectiveness of the intervention will be expressed in terms of cost per complication avoided. The time horizon of the study will be at most one year and nine months, corresponding to the period of pregnancy and a one-year post-delivery follow-up period. Given the relatively short duration of follow-up, costs and effectiveness will not be updated. In addition to data collected in the CRF, all direct medical costs up to one year post-delivery will be retrieved from the National Health Insurance

database.

Qualitative assessment method.

Practical aspects

Women will be selected after delivery according to their medical follow-up during pregnancy.

Every woman included in the NAITRE study is eligible for the qualitative study except in case of stillbirth, postnatal death or if the baby suffers from a seriously condition. As the women should be in position to relate their pregnancy, it seems it would be difficult for women in mourning.

To ensure adequate representativeness, women will be selected in both the intervention and control group to obtain different ages, primiparous and multiparous women, different economic conditions, and different adherence to prenatal care. This information is given by investigators after the delivery. Semi-directed individual interviews will aim to understand the determinants of medical follow-up during pregnancy. The principle is to get the respondents to describe situations that highlight their habits, their social representations or their emotions. Women will be asked to describe their health practices during pregnancy, what was important for their medical follow-up, what led them to renounce scheduled care. For women who received the financial incentive, it is also a question of asking them how they experienced this incentive and what it may or may not have brought them.

In order to get this information, a retrospective study will be conducted. Interviews will take place within one month of delivery. Women will be invited to return to the referral centre or will be seen at their home (with a specific incentive of €40 credited to the card for those in the intervention group, or a payment card for those in the control group).

The method of semi-structured individual interviewing is based on an interview guide containing closed or open questions, designed so as not to be inductive with regard to the themes to be explored. Interviews will begin with an open-ended question: "*Can you tell me about your pregnancy*?".

Depending on the construction of the interviewee's story and according to the logic of a dialogue, the

questions of the interview guide will be asked only if the information has not been provided spontaneously. These questions will be grouped in an interview guide available to the interviewer at the time of the interview with the respondent. These interview guides are constructed in such a way so as to favour a more or less long interview depending on the interviewee (about 1 hour), using simple, easily understandable questions.

Whenever necessary, the interview will be conducted with the assistance of an interpreter (telephone interpreter, planned budget).

Interview grid for the qualitative survey is shown, in French language only, in annex 3.

Method of collection

The respondents will be met individually in a confidential location. Interviews will be conducted by a social scientist trained in qualitative research. Women will be asked to allow the interview to be recorded, transcribed and analysed anonymously.

Methods: assignment of intervention

Allocation.

Centres are randomly allocated to two-month periods of either the intervention or control group. Randomization is centrally generated, and before the end of a period, centres are not aware of the group they will be allocated to for the next period, in order to prevent the postponement of inclusions at the end of one control period so as to include women in the next intervention period.

The inclusion of women and the reporting of further pregnancy follow-up visits are made through a web-based eCRF (www.etudenaitre.fr), where the information sheet and consent form, translated in 18 foreign languages, can be downloaded directly. Women will be included prospectively by obstetricians and midwifes in the participating centres, based on their type of health insurance coverage

Blinding

By the nature of the study, blinding of the intervention is not feasible. But all analyses will be conducted by a statistician blinded to allocation to the intervention or control group.

Methods: Data collection Management and Analysis,

Data collection methods.

Data will be collected through the eCRF. Inclusion and non-inclusion criteria, as well as attendance at each scheduled visit in the intervention group, will be prospectively entered into the eCRF. All other data, for maternal and neonatal outcomes, will be extracted from individual pregnancy records, in each of the participating centres, and collected into the eCRF by clinical research assistants.

For the cost-effectiveness study, data for the first year of life will be extracted from the French Hospitalisation (PMSI) and Health Insurance (SNIIR-AM) databases, and analysed at Dijon University Health Centre

Data management.

The data will be managed by the Clinical Investigation Centre (CIC INSERM 1432) at Dijon University Hospital.

Statistical method

Descriptive analysis

Clinical and demographic characteristics of the women will be presented, and the comparability of the two groups of women regarding pregnancy risk factors will be assessed.

Primary outcome analysis

The primary criterion, as described previously, is binary. The principal analysis will be a proportion

comparison using the Chi-squared test adjusted for the design effect, on an individual basis.

As the cluster randomization will generate a lower quality of balance between covariates, we will additionally study the following parameters, which potentially interfere with maternal or foetal outcomes, using univariate logistic regression:

- type of centre (local / intermediate risk / high-risk maternity unit)
- proportion of deprived women in the centre (three levels defined as <25th, 25th -75th and >75th percentile of the observed proportions in the different centres)
- age (<20, 20-35, >35 years old)
- parity (0, 1 or 2, more than 2)
- type of free healthcare (CMU-C/AME)

Interactions of these parameters and the effect of the intervention will be searched for using sub-group analyses.

A multivariable multilevel logistic regression adjusted for all the covariates with a p<0.20 will then be performed, taking into account the eventual interactions. A random effects term referring to clusters will be included in the model. The multivariate building process will use a stepwise approach. For each step, the Akaike information criterion (AIC) scores will be calculated to measure the relative goodness of fit of the different models, where the lower the AIC, the better the fit. The model with the lowest AIC score will be retained for the analyses.[29]

Secondary outcome analysis

1. Adverse outcomes in the child: same as the principal analysis, using this outcome.

2. Adverse outcomes in the mother: same as the principal analysis, using this outcome.

3. The number of prenatal consultations following the HAS standard care recommendations will be analysed using weighted means taking into account the cluster randomisation.

An intermediate analysis will be performed after the first phase, but using a significance level of 0.0001 in order not to impair the study power.

Significance threshold

The results will be considered statistically significant if $p<0.05$.

Statistical software

The analyses will be performed using SAS software, latest version at the time of analysis. Statisticians will be blinded to the study groups

Analysis of qualitative survey.

Raw data are analysed according to a thematic analysis method. From this progressive work of conceptualization and continuous comparison of the different situations, a theoretical system responding to our problems will be defined. A triangulation of data will be done as two sociologists will code the interview transcriptions. Nvivo software, which allows the creation of a code, and has been well validated for qualitative analyses, will be used.[30] Qualitative data will be analysed during the data collection. The collection of data will continue until concept saturation is reached. Theoretical saturation will be assessed.[31] Practically, saturation is reached when no new data could add more information to meet the research objectives. Data will be analysed by two researchers and the collection of data will end when two consecutive interviews have not generated any new information.

Statistical analysis of cost effectiveness.

A differential cost-effectiveness ratio associated with the intervention versus no intervention will be calculated by comparing the difference in average costs with the difference in average efficiencies. In order to test the robustness of the conclusions drawn, sensitivity analyses will be carried out on the

parameters likely to have an influence on the results.

A nonparametric bootstrap analysis of the cost and efficiency differential observed between the two strategies will allow uncertainty to be taken into account and to estimate 95% confidence intervals for the differential ratios of the baseline analysis.

Methods: Monitoring

Monitoring

As the study has been deemed non-interventional by the ethics committee, legally no formal monitoring is requested. Nonetheless the study will be monitored for quality and regulatory compliance. The monitoring will be supervised by the promoter (Dijon-Bourgogne University Hospital) in all of the participating centres. The frequency depends on inclusion rates, questions and pending issues from earlier audits: once or twice a year.

Harm

Steering and Data and Safety Monitoring Committees(DSMC):

The coordinating centre at CHU Dijon-Bourgogne, Centre d'Investigations Cliniques (CIC INSERM 1432), takes responsibility for all aspects of the study: ethical, regulatory, study conduction, data-management and publication strategy.

The steering committee is composed of the principal investigators of the first 10 centres, one representative from each perinatal care network involved in the study, a midwife, a social worker and a methodologist. A phone meeting is held every four months. The role of the steering committee is to ensure that the study is running according to study protocol and to share solutions to overcome difficulties in recruiting participants.

The data monitoring and safety committee (DSMC) is composed of two obstetricians, who specifically

take care of socioeconomically disadvantaged women, a methodologist, an ethics specialist, and a paediatrician. The DSMC will essentially review results of the qualitative survey conducted during the first year, and follow observed versus expected, recruitment curves. If the qualitative survey were to suggest that the intervention stigmatizes women, the scientific committee will have the right to stop the study. As women will be managed according to French guidelines during their antenatal and post-natal period and will thus not be affected by the study, not harm other than potential stigmatisation is expected. No interim analysis has been planned, as it would have had a significant impact on sample size.

Auditing.

The study has been deemed non-interventional by the Ethics Committee; as a result, by law no formal auditing will be conducted.

Ethics and dissemination

Research Ethics approval.

Ethics approval was given by the Dijon Ethics Committee (CPP Est-1) on September 18th 2014, and the protocol was amended thereafter.

The study obtained funding from the French Ministry for Health in December 2014 (PREPS-14-0173) and the study is promoted by Dijon Bourgogne University Hospital (France).

Authorization for holding the computerized databases was granted on March 21st 2016 by the National Committee for Informatics and Freedom (CNIL). This long delay was due to conflict between the reasoning of the CNIL, for which the preservation of private life is its top priority, and the French source of public funding, which needs to know precisely to whom public money, in this case the financial incentive, is being given.

It was registered in Clinicaltrials.gov with the identifier NCT02402855, on March 17th, 2015, at the

French Research Agency with identifier 2014-A01319-38, and at the CNIL with request for authorization n°915385.

Protocol amendments.

The study is currently running according to the 5th amended version, June 30th 2016.

Consent or assent.

The study is non-interventional according to first approved version of the protocol, no formal consent is required to be recruited.

Formal consent, from the women only, is requested for the collection of data concerning their children. (See information sheet in appendices)

Declaration of interests

The authors of the present paper have no competing interest to disclose.

Access to data:

Authors have no data to share at this stage. For reviewing purposes, data will be shared with reviewers, and once a paper has been published, data will be made available for scientific purposes.

Ancillary and post-trial care.

As the study does not affect the usual care of women, no post-trial care has been scheduled. No ancillary studies have been planned so-far

Dissemination policy.

A manuscript with the results of the primary study will be published in a peer-reviewed journal. Separate manuscripts will be written on each of the secondary aims, and these will also be submitted for publication in peer-reviewed journals.

The results will be presented at scientific meetings, and specific communication will be organised to target health professionals, policy decision-makers, regulatory bodies, and women.

Recruitment is on-going; the first women were recruited on June 4th 2016 in the control group and on June 10th 2016 in the intervention group.

Discussion.

This will be the first study to provide rigorous evidence regarding the effectiveness of financial incentives to improve the use of prenatal care and their impact on perinatal outcomes for the mother and the foetus. A recent Cochrane meta-analysis[23] emphasized the need for such an assessment, and it is of particular interest to note that no such studies have been carried in Europe so far.

The conditional cash-transfer is not supposed to replace any other public health policies aimed to promote appropriate prenatal care but it may help to overcome some of the barriers that stand in the way of adequate follow-up. Most of the studies have been conducted in low-income countries, where, besides many other factors, the structure of the health care system and health care facilities are very different from those in developed Countries.

For example, in 2005, the Indian Government implemented the Janani Suraksha Yojana program, which incentivizes poor women to give birth in a health facility by providing them with a cash transfer upon discharge. There was, however, no formal assessment of the efficacy. Whereas this program was associated with a very significant increase in the rate of delivery in health care facilities (from 39% to 74%), a recent survey suggested that beyond the cash incentive, the shift in the social norm and the women's own perception played a major role in this effect.[32] Interestingly, this program was shown to

be associated with a reduction in neonatal and perinatal deaths.[33]

Financial incentive programs to promote smoking cessation during pregnancy have been assessed and have recently been reported to be associated with a reduced likelihood of low-birth weight.[34]

If our intervention proves to be effective, its implementation may have to overcome several difficulties, including tailoring the intervention to women most likely to respond, increasing acceptability of the concept among public bodies and health professionals, and proving the intervention to be cost effective. It has been suggested that for some interventions, efforts have to be made to increase acceptability, even when they have been proven to be effective.[35] All of these aspects will be covered by our research program.

The investigators have no conflicts of interest to declare.

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CHU Besançon, Pr Didier Riethmuller, Dr Aude Bourtembourg, Dr Nicolas Mottet, Dr Claire Toubin, Guillaume Boiteux

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Contributorship statement:

Study design: Bardou M, Crépon C, Bertaux A-C, Godard-Marceaux A, Duflo E, and Le Ray I..

Obtaining funding and drafting publication: Bardou M,

Reviewing and amendment of the protocol, reviewing of the paper: Eckman-Lacroix A, Thellier E, Falchier F, Deruelle P, Doret M, Carcopino-Tusoli X, Schmitz T, Barjat T, Morin M, Perrotin F, Hatem G, Deneux-Tharaux C, Fournel I, Laforet L, Meunier-Beillard N

Authorship eligibility guidelines and any intended use of professional writers. Marc Bardou will be first author of the main publication of study results, he will be last author of affiliated papers, if any, such as results of the qualitative and the cost effectiveness surveys. Godart-Marceau A, will be first author of the qualitative survey and Bertaux AC of the cost effectiveness study. Bardou, M will sign as last author. One investigator will be listed as an author in each of the participating centres, with the investigator of the best recruiting centre (based on the number of participants recruited pro-rata with the time spent by the centre on the study and the number of pregnancies followed during that time). We do not intend to use a professional writer.

Funding:

The study has been funded by the Ministère de la Santé, Ditection Générale de l'Ofrre de Soins (DGOS) (Grant number PREPS-14-0173).

Sponsor: CHU Dijon-Bourgogne, Délégation à la Recherche Clinique et à l'Innovation.

Sponsor Contact Person: Catherine Renaud, tel + 33 380 29 31 53; catherine.renaud@chu-dijon.fr

Neither funder nor sponsor had any role in the study design, writing of this report, or the decision to submit the report for publication.

Supplementary files.

Annex 1 and 2. Information and consent sheets forms for the intervention and control groups respectively.

Annex 3. Interview grid for the qualitative survey

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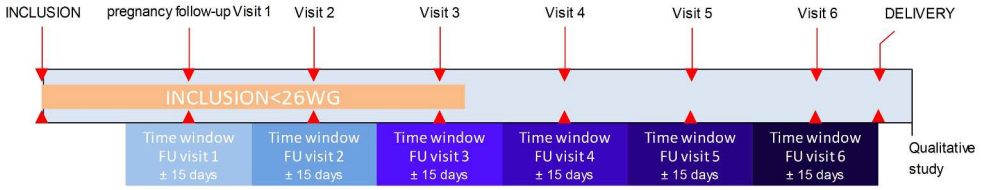
Figure legends.

Figure 1. Scheduled prenatal care visits and time window for financial incentives. If a women shows up for a scheduled more than 2 weeks after her standard pre-planned visit, she will receive the incentive for the next visit. This means that she will not attend a scheduled visit without receiving an incentive (with the limit of no more than one incentivised visit per month), but she may receive fewer incentive paymants than the maximum she could have obtained.

Figure 2. Overall management of women, according to their allocation group. CRA = Clinical Research Assistant.



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319x61mm (300 x 300 DPI)

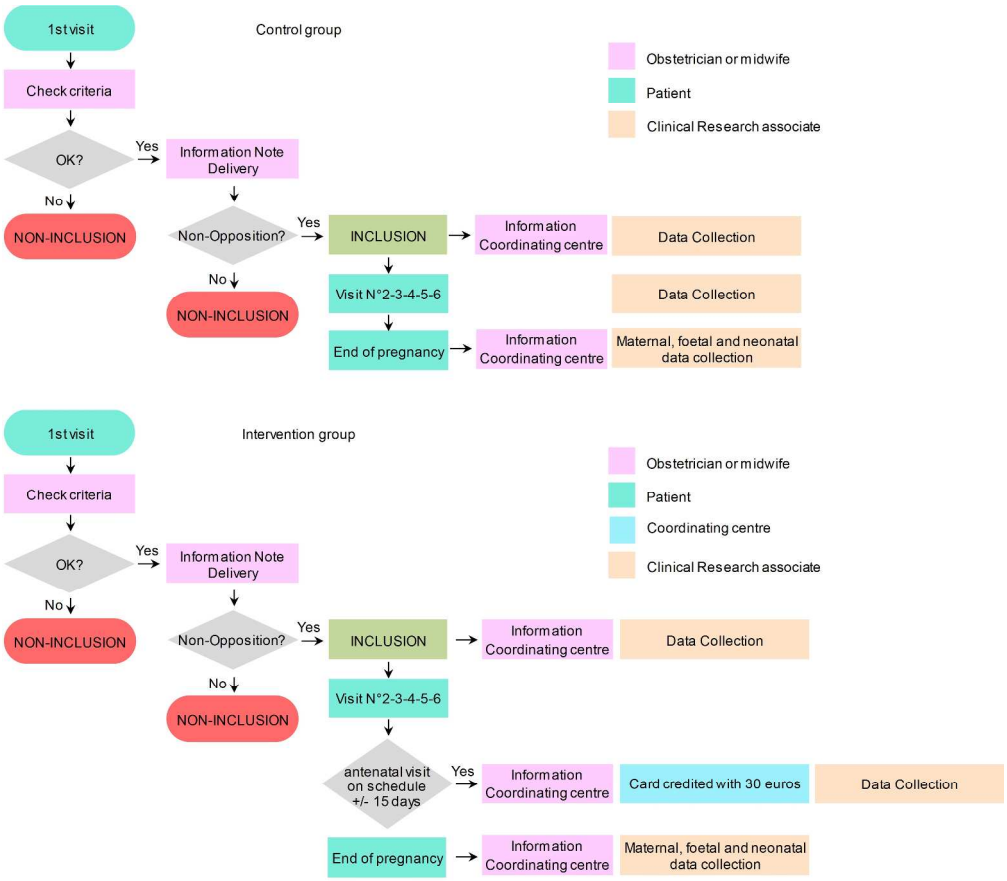

Figure 2. Overall management of women, according to their group of allocation. CRA = Clinical Research Assistant.

304x266mm (300 x 300 DPI)

Référence Etude / Study Reference : NAITRE
Note d'information / Information Sheet : Version n° 04 (30/06/2016)

Information sheet

Evaluation of the impact of financial support on the medical follow-up and pregnancy outcomes in pregnant women who benefit from CMU, CMU-C or AME

Registration N°: 2014-A01319-38

Organizer of the research project: ***Dijon University Hospital***

Person directing and supervising the research: ***Professor Marc BARDOU**, medical coordinator of the Clinical Investigation Centre 1432, plurithematic module*

Madam,

Your doctor has suggested you take part in research aiming to evaluate care currently provided by Dijon University Hospital. Before making your decision, it is important for you to read the following pages attentively. They will provide necessary information concerning the different aspects of this research. Feel free to ask any questions you wish.

Your participation in this research is entirely voluntary and you have the right to refuse to take part. In such a case, you will continue to benefit from the best medical care possible, in accordance with current knowledge.

Why this research?

The frequency of complications in pregnancy, such as the prematurity or low birth weight, is almost 50% higher in women who depend on social support than in those whose revenue comes from their work.

These high-risk pregnancies should be particularly well followed so as to detect and treat complications early. Universal Medical Cover (CMU), CMU-C (complementary) and State Medical Aid (AME) ensure that people who meet specific French government criteria have access to health care. However, a third of those entitled to CMU refuse care for financial reasons and ¼ of female patients who rely on welfare support have fewer than 7 consultations during their pregnancy. The recommendations of the health authorities (Haute Autorité of Santé) on the minimal follow-up are thus not respected.

What is the aim of this research?

To determine whether financial support provided on condition that patients respect at least the minimum recommendations of the Health Authorities can reduce the rates of pregnancy complications, for the mother and her child, for pregnant women who benefit from CMU, CMU-C or AME (state of health during their pregnancy, and that of the baby at birth).

How is the research organized?

You have come to the hospital to declare your pregnancy. You will have a medical examination with regard to your pregnancy. The results of this examination will be given to you.

The medical team will propose medical follow-up for your pregnancy in accordance with Health Authority recommendations, which means attending at least 7 follow-up consultations during your pregnancy.

You will be given € 30 (thirty euros) for each of the scheduled follow-up visits (**6 maximum**) you attend, if they are done according to your doctor's recommendations. This money will be given in the form of a payment card at the next consultation. The card will be credited after each of the **follow-up consultations** scheduled by your doctor or the midwife who is following your pregnancy **you attend** (**other than emergency consultations, other than follow-up consultations for illness**).

You will have no other additional medical examinations (consultations, echography, blood tests) because of the research.

Emergency consultations will not give rise to financial compensation.

If the state of your pregnancy requires specific management involving **more frequent consultations, no additional financial compensation will be provided**.

What do you have to do?

If you accept, we will collect in a strictly anonymous manner the information in your medical record concerning your medical history, your ethnic origin, the follow-up of your pregnancy and the delivery, your state of health and that of your child.

What are the possible drawbacks?

Your participation will have no impact on the medical care provided by the medical team.

What are your rights?

This study has been approved by the ethics committee "Comité de Protection des Personnes (CPP) Est I", le 28/10/2014.

This study will be carried out in accordance with the law on medical secrecy "informatique et liberté" (*la loi du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés* modifiée par la *loi du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements des données à caractère personnel*) (the law of 6 January 1978 relative to computerized information, to files and liberty modified by the law of 6 August 2004 relative to the protection of persons with regard to the processing of personal data).
You have the **right to see and to rectify** your computerized records and to **oppose** the transmission of your data used in the context of this study. These rights can be exercised by contacting the coordinating centre for the study (at the address and telephone number below).

Your medical and personal data will be processed by computer to analyse the results. The processing will be anonymous and confidential as your data will be identified only by your initials associated with a code number. The data will be transmitted to the research organizer.

At any time during the study, you can contact the investigating doctor to obtain any additional information you may need about the study, about your participation or about your personal health data.

If you wish, you can be informed about the overall results of the research at the end of the study by the coordinating centre.

The results of this study may be used for communications and/or published in scientific journals. Your identity will not appear in these.

Your participation is voluntary and of your own free will

Your refusal to take part will have no impact on the type and the quality of your care, or on your relationship with the medical team.

If you accept to take part, you can leave the study at any time without giving a reason. Leaving the study will have no impact on the quality of your care.

The information collected before you leave the study will be used unless you do not wish so. In this case you must inform the investigating doctor.

Thank you for your cooperation.
If you agree to take part in this study,
please give your verbal agreement.

Investigating Centre / Centre Investigateur :

Logo of the centre/ Etiquette centre :
Identity of the Principal Investigator/ Identité Investigateur Principal :
Address / Adresse :
Telephone/ Téléphone :

Coordinating Centre / Centre coordonateur :

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14 rue Paul Gaffarel,
BP 77908, 21079 DIJON CEDEX;
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Exemplaire à remettre à la patiente

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Anglais / INTERV

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Anglais / INTERV

Etude NAITRE - Auto-questionnaire à compléter par les patientes au moment de leur inclusion

Identification patiente (n° de centre – n° d'inclusion dans le centre) : |__||__| - |__||__||__||__|

Madame,

Vous avez accepté de participer à l'étude NAITRE sur le devenir de la grossesse chez des femmes bénéficiaires de la CMU, de la CMU-C ou l'AME. Nous vous remercions de bien vouloir répondre aux questions suivantes.

Rencontrez-vous parfois un travailleur social ?	☐ OUI / ☐ NON
Bénéficiez-vous d'une assurance maladie complémentaire ?	☐ OUI / ☐ NON
Vivez-vous en couple ?	☐ OUI / ☐ NON
Êtes-vous propriétaire de votre logement ?	☐ OUI / ☐ NON
Y-a-t-il des périodes dans le mois où vous rencontrez de réelles difficultés financières à faire face à vos besoins (alimentation, loyer, EDF…) ?	☐ OUI / ☐ NON
Vous est-il arrivé de faire du sport au cours des 12 derniers mois ?	☐ OUI / ☐ NON
Êtes-vous allée au spectacle au cours des 12 derniers mois ?	☐ OUI / ☐ NON
Êtes-vous partie en vacances au cours des 12 derniers mois ?	☐ OUI / ☐ NON
Au cours des 6 derniers mois, avez-vous eu des contacts avec des membres de votre famille autres que vos parents ou vos enfants ?	☐ OUI / ☐ NON
En cas de difficultés, y a-t-il dans votre entourage des personnes sur qui vous puissiez compter pour vous héberger quelques jours en cas de besoin ?	☐ OUI / ☐ NON
En cas de difficultés, y a-t-il dans votre entourage des personnes sur qui vous puissiez compter pour vous apporter une aide matérielle ?	☐ OUI / ☐ NON

Quelle est votre durée quotidienne de transport pour vous rendre à votre travail **(temps aller-retour domicile-travail) ?**	☐ sans activité professionnelle ou ☐ inférieure ou égale à 30 min (≤30 min) ☐ entre 30 min et 60 min (> 30 min et ≤ 60 min) ☐ entre 1 h et 2h (> 1h et ≤ 2h) ☐ supérieure à 2 h (> 2h)

Quel mode de transport avez-vous utilisé pour vous rendre à cette consultation de suivi de grossesse ?	☐ Véhicule personnel ou véhiculée par un proche (famille, ami) ☐ Transports en commun (bus, métro, train, …) ☐ Autre moyen de transport → précisez : _ _ _ _ _ _ _ _ _ _ _ _

Information sheet

Medical follow-up and pregnancy outcomes in pregnant women who benefit from CMU, CMU-C or AME

Registration N°: 2014-A01319-38

Organizer of the research project: ***Dijon University Hospital***

Person directing and supervising the research: ***Professor Marc BARDOU**, medical coordinator of the Clinical Investigation Centre 1432, plurithematic module*

.

Madam,

Your doctor has suggested you take part in research aiming to evaluate care currently provided by Dijon University Hospital. Before making your decision, it is important for you to read the following pages attentively. They will provide necessary information concerning the different aspects of this research. Feel free to ask any questions you wish.

Your participation in this research is entirely voluntary and you have the right to refuse to take part. In such a case, you will continue to benefit from the best medical care possible, in accordance with current knowledge.

Why this research?

Universal Medical Cover (CMU), CMU-C (complementary)) and State Medical Aid (AME) ensure that people who meet specific French government criteria have access to health care. However, certain beneficiaries may avoid seeking care, especially during pregnancy. The same is true for persons covered by the National Health Insurance Scheme but without private mutual health insurance. We wish to describe these situations, as well as their consequences for the mother and child.

What is the aim of this research?

To collect information concerning pregnant women who benefit from CMU, CMU-C or AME (state of health during their pregnancy, and that of the baby at birth).

How is the research organized?

You have come to the hospital to declare your pregnancy. You will have a medical examination with regard to your pregnancy. The results of this examination will be given to you.
The medical team will propose medical follow-up for your pregnancy in accordance with Health Authority recommendations, which means attending at least 7 follow-up consultations during your pregnancy.
Your medical follow-up will follow the normal process as planned by the doctor or midwife will follow you, with no involvement of the research team. If you accept, we will collect in a strictly confidential and anonymous manner the information from your medical record concerning your medical history, your ethnic origin, the follow up of your pregnancy and your delivery, your state of health and that of your baby.

You will have no other additional medical examinations (consultations, echography, blood tests) because of the research.

What are your rights?

This study has been approved by the ethics committee "Comité de Protection des Personnes (CPP) Est I", le 28/10/2014.

This study will be carried out in accordance with the law on medical secrecy "informatique et liberté" (*la loi du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés* modifiée par la *loi du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements des données à caractère personnel*) (the law of 6 January 1978 relative to computerized information, to files and liberty modified by the law of 6 August 2004 relative to the protection of persons with regard to the processing of personal data).

You have the **right to see and to rectify** your computerized records and to **oppose** the transmission of your data used in the context of this study. These rights can be exercised by contacting the coordinating centre for the study (at the address and telephone number below).

Your medical and personal data will be processed by computer to analyse the results. The processing will be anonymous and confidential as your data will be identified only by your initials associated with a code number. The data will be transmitted to the research organizer.

At any time during the study, you can contact the investigating doctor to obtain any additional information you may need about the study, about your participation or about your personal health data.

If you wish, you can be informed about the overall results of the research at the end of the study by the coordinating centre.

The results of this study may be used for communications and/or published in scientific journals. Your identity will not appear in these.

Your participation is voluntary and of your own free will

Your refusal to take part will have no impact on the type and the quality of your care, or on your relationship with the medical team.

If you accept to take part, you can leave the study at any time without giving a reason. Leaving the study will have no impact on the quality of your care.

The information collected before you leave the study will be used unless you do not wish so. In this case you must inform the investigating doctor.

Thank you for your cooperation.
If you agree to take part in this study,
please give your verbal agreement.

Investigating Centre / Centre Investigateur :

Logo of the centre/ Etiquette centre :
Identity of the Principal Investigator/ Identité Investigateur Principal :
Address / Adresse :
Telephone/ Téléphone :

Coordinating Centre / Centre coordonateur :

DIJON CHU,
Centre d'Investigation Clinique 1432-Plurithematique,
14 rue Paul Gaffarel,
BP 77908, 21079 DIJON CEDEX;
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Référence Etude / Study Reference : NAITRE
Formulaire de consentement au recueil et au traitement des données / Version n° 01 (28/12/2015)
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Ouverture de l'entretien

Grille d'entretien

Moment de l'entretien : lors de la visite post natale (6 semaines après l'accouchement)

Lieu de l'entretien : Domicile ou centre de consultation

Présentation du chercheur

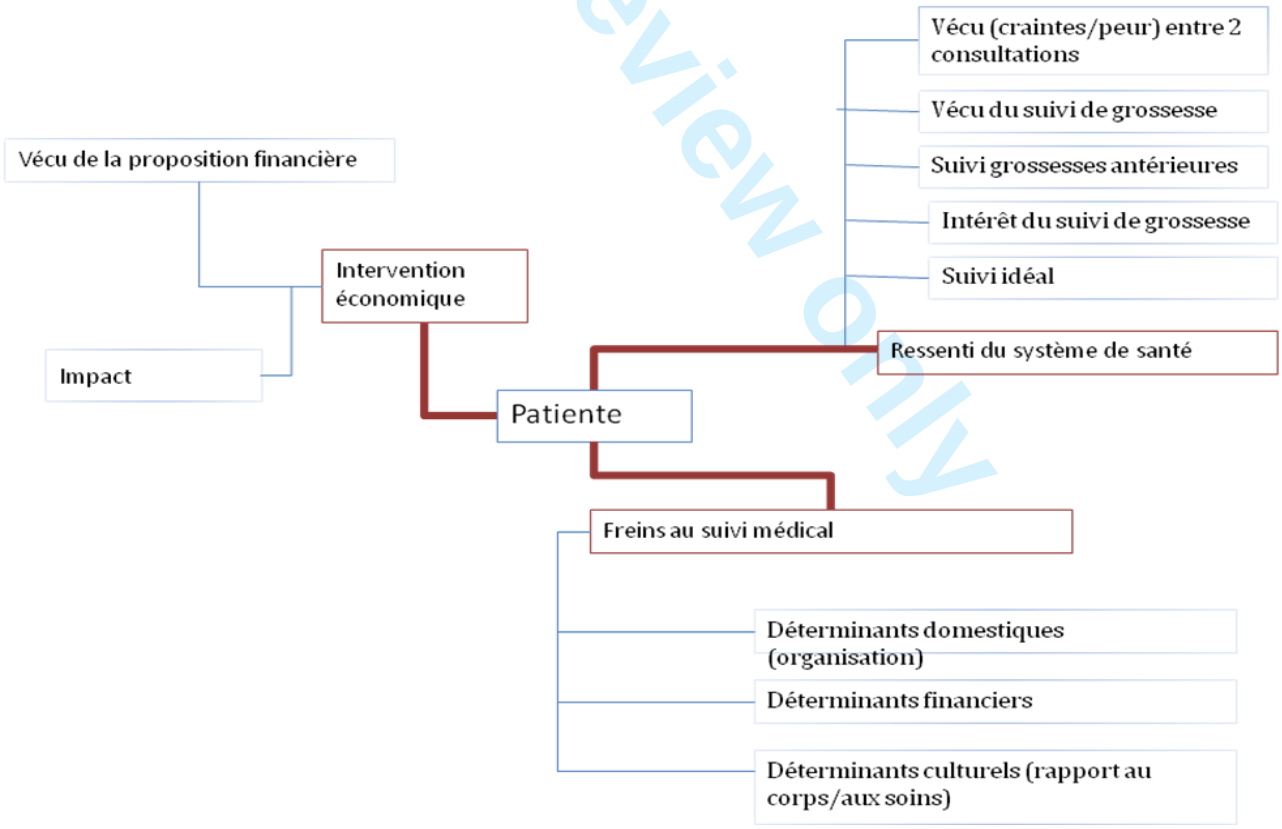
Rappeler leur inclusion dans une étude.

Rappeler qu'on est chercheur.

Objet de l'entretien : vécu de la participation dans cette étude.

Schéma de l'entretien

Selon les informations dont nous disposons en amont**, l'entretien pourrait se terminer** par quelques questions sur l'histoire de vie des femmes rencontrées.



Pouvez-vous me raconter comment s'est déroulée votre grossesse ?
Renoncement aux soins Quelles ont été les difficultés que vous avez rencontrées pour assister à ces consultations ?
Ressenti du suivi médical Le ministère préconise 7 visites médicales et 3 échographies, que pensez-vous de ces préconisations ?
Impact de l'intervention A votre avis, qu'est-ce qui vous aurait aidé à assister au nombre de consultations recommandé ? ➔ Pour les femmes appartenant au bras hors intervention : Si une compensation financière vous était proposée pour chaque rendez-vous effectué, qu'en penseriez-vous ? Quelle utilisation en auriez-vous fait ? Quelle somme pourrait- être proposée ? ➔ Pour les femmes appartenant au bras invention : Que pensez-vous de la proposition faite par le médecin de vous remettre une carte créditée pour chaque visite médicale effectuée ? Quelle utilisation en avez-vous fait ? Que pensez-vous de la somme qui vous été donné ? (beaucoup, pas assez ?)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ☑
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ☑
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier ☑
Funding	4	Sources and types of financial, material, and other support ☑
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor ☑
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities ☑
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) ☑
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ☑
	6b	Explanation for choice of comparators ☑
Objectives	7	Specific objectives or hypotheses ☑
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) ☑

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained ☑
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ☑
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ☑
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) ☑
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ☑
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial ☑
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended ☑
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) ☑
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations ☑
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ☑

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions ☑

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned ☑
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions ☑
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how ☑
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial ☑
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol ☑
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols ☑
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol ☑
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol ☑
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) ☑
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) ☑
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed ☑

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ☑
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ☑
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ☑
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ☑
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ☑
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ☑
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable ☑
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ☑
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ☑
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ☑
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation ☑
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions ☑
	31b	Authorship eligibility guidelines and any intended use of professional writers ☑
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **NA**

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ☑
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **NA**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.