RESILIENT

Shaping the best future for maternity services

Post-pandemic planning for maternity care for local, regional, and national maternity systems across the four nations

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1. TITLE

Post-pandemic planning for maternity care for local, regional, and national maternity systems across the four nations

2. SUMMARY OF RESEARCH

The UK has the fifth-highest burden of COVID-19 cases and related deaths of any country in the world, with more than 4.3 million cases and 125,000 associated deaths as of 11/Apr/2021. In response, the National Health Service (NHS) has undertaken substantial maternity and other service modifications. The rapid roll-out of the COVID-19 vaccination programme has dramatically altered the trajectory of the pandemic and given considerable hope; however, we will continue to deal with the pandemic and its aftermath for the foreseeable future. For example, questions remain about lasting immunity after vaccination beyond six months, effectiveness against new variants, vaccination uptake, and whether annual vaccination (as for influenza) will be required.

Maternity care is a core service of the NHS. Substantial service reconfiguration was undertaken during the pandemic, in response to local infection rates and lockdown measures. While there were adverse pregnancy outcomes related to COVID-19 infection[1], there are indications of indirect effects on outcomes, good and bad[2].

Acceptance of COVID-19 vaccination by pregnant women is uncertain, as they: were excluded from all vaccine trials, and are risk-averse, even when those risks are unlikely but unknown[3]. Moreover, acceptance of vaccination in the general community is not uniform, and is particularly low among Black, Asian and Minority Ethnic populations who are at heightened risk of severe infection. Guidance has changed rapidly, and the precautionary principle of needing evidence of no harm before recommending COVID-19 vaccination in pregnancy has weighed heavily in some recommendations[3].

In this two-year project, we seek to study the impact on pregnancy outcomes of COVID-19 pandemic-related maternity service reconfiguration, and how we can 'Build Back Fairer' post-pandemic to reduce inequalities in maternity care (Fig 1). The service reconfigurations of particular interest are virtual maternity care, out-of-office monitoring (of blood pressure [BP] and blood glucose) and COVID vaccination (Objective 1). Across these three areas, we will study whether changes magnified or diminished existing inequalities in maternity care for minority ethnic group women or those living with social or medical complexity, including subfertility or mental health (Objective 2). Finally, we will engage with stakeholders to develop policy for local, regional, and national health systems across the four nations (Objective 3). This will be accomplished through three work packages (WPs), below.

Fig 1: Overview: post-pandemic planning for maternity care

Legend: ***CSS*** COVID Symptom Study Biobank; ***eLIXIR*** early-LIfe data cross-LInkage in Research; ***IDI*** in-depth interview; ***WP*** Work Package

WP1 (Magee, Lead): QUANTITATIVE methods to describe, quantify and explain using routinely-collected, linked maternity and offspring data in the MRC-funded early-LIfe data cross-LInkage in Research (eLIXIR) platform (≈35,000 records), from three Trusts in an

ethnically- and socially-diverse area, South London. We will describe and quantify temporal trends in relevant health outcomes and costs (NHS perspective), by service configuration and inequalities (as above), using segmented and individual-level multivariate regression. We seek a coherent pattern of results to be interpreted in light of WP2 findings.

WP2 (Silverio, Easter, and Duncan co-Leads, Magee Chair): SOCIAL SCIENCE to enrich understanding of quantitative data. In-depth interviews (IDIs) with a maximum diversity sample of pregnant/postpartum women, partners, care-providers, and policy-makers, with lived experience of receiving/providing maternity services during the pandemic. The interview schedule will explore what changed in care, what it meant to them, and whether they were confident about the care received/offered (including vaccination). Analysis will be by qualitative methods (eg, thematic framework analysis).

Also, questionnaires will be administered to maternity service users nationally (≈43,000) via the King's College London COVID Symptom Study app with ZOE Global Ltd. (KCL-CSS/ZOE app), to gather data about vaccine hesitancy (including whether views were preformed or related to care experiences), uptake, and side effects, and subsequent COVID-19 infection, among women who are planning pregnancy, pregnant, or postpartum.

WP3 (Nelson, Lead): STAKEHOLDER ENGAGEMENT within local, regional, and national maternity systems, to identify lessons learnt, high-impact actions and illustrative case studies. Regional listening events ('imagining our best future') are planned in each UK nation to: assess WP1 and WP2 evidence; explore what worked and should be retained; what did not work and should be reversed; brainstorm, shortlist, and prioritise high-impact future actions; and understand facilitators and barriers to action implementation. A national Policy Lab ('co-production for action') will explore listening event findings, and produce an 'imagine our best future' report for dissemination.

We have a multidisciplinary team experienced in maternity care and COVID-19 (Magee, von Dadelszen, Khalil), midwifery (Bick), PPIE (Newburn), out-of-office monitoring (White, Khalil, Duncan), maternal mental health (Easter), public health and paediatrics (Wolfe), routinely-collected data (Poston, Khalil, Nelson), statistics (Seed, Molteni), qualitative science (Silverio, Easter), real-time epidemiology (Duncan), health economics (Fox-Rushby, Soley-Bori), primary care (Elwyn), and policy (Nelson, Van Citters, Boulding). Our collaborators will support with additional expertise in: infertility (Duffy), paediatrics and lived experience of Long COVID (MacDermott), KCL-CSS/ZOE app (Steves), policy and transferability of findings nationally (Duffy, Reynolds) with Khalil, service user perspective (Brewin), and risk communication during pregnancy (Hodson). (For details, see Section 10.)

This work will inform the care of more than 600,000 UK pregnancies/year, and at least as many women planning pregnancy. We will disseminate our findings through established networks of local, regional, and national stakeholders. Our strategy includes engagement events across the four nations, virtual engagement via webinars and social media, and publication of a bespoke plain-language and scientific website and report.

Our impact will be broad, on:

- Individual patients: improve care quality (effectiveness, safety and experience);
- NHS maternity providers: strengthen evidence to inform service reconfiguration and support vaccination role-out;
- NHS Long Term Plan: address maternal and fetal/newborn death and morbidity and support implementation of digitally-enabled care;
- Wider society: innovation to commercialise and decrease direct and indirect societal costs.

3. BACKGROUND AND RATIONALE

Our literature review was based on our and others recent published systematic reviews of direct (published and 'living') and indirect effects of the pandemic on maternal and offspring outcomes and service reconfiguration. Searches included major databases (eg, Medline, Embase, and Cochrane) and used (MeSH) terms, keywords, and word variants for 'COVID-19' and 'pregnancy', restricted to 2019-21 but not language. We undertook a new Medline

search for UK health economics literature [(spend* or expenditure* or cost* or utlilization or hospital* or visit* or appointment* or demand*).ti,ab.) for virtual care or out-of-office monitoring [('tele* or virtual* or monitor* or home*).ti.] in pregnancy in English (29/Mar/2021).

Initial concern about the impact of the pandemic on pregnancy was focussed on potential vulnerability of pregnant women to infection and associated complications, as in prior coronavirus and influenza outbreaks[4]. Reassuringly, pregnant women (vs. others of reproductive age) are not more likely to become infected with COVID-19, with the possible exception of ethnic mintorities[5]. If pregnant women do get COVID-19, their symptoms are similar, but more frequently lead to hospitalisation based on KCL-CSS/ZOE app findings[6].

It is estimated that of the 712,000 UK births/year (2019), one in 10 pregnant women become infected with COVID-19, based on 'living' systematic review (73 cohort studies, 20/Nov/2021)[7]. Most (≈75%) of these women are asymptomatic and identified by universal screening in place by May/2020 in UK maternity units.

Symptomatic COVID-19 positive (vs. negative) pregnant women have been more likely to: develop severe COVID (≈10%); require intensive care (≈4%) or mechanical ventilation (≈3%), particularly when they have co-morbidities (see below); deliver preterm (≈17%) or by Caesarean (≈54%); and have babies who require neonatal unit admission (≈33%) (95 studies)[1 7 8]. Systematic review focussed on COVID-19 severity has endorsed earlier concern about an excess risk of pregnancy hypertension, particularly with severe COVID-19, as well as an increased risk of gestational diabetes mellitus (GDM) and low birthweight (42 studies, 29/Jan/2021)[9 10]. Recent UK Obstetric Surveillance System (UKOSS) data showed that even asymptomatic COVID-19 positive women (vs. historical controls) were more likely to be delivered by Caesarean (≈40%) or operative vaginal delivery (≈14% women)[5].

There are subgroups of pregnant women at particular risk of severe COVID-19, based on systematic review and UKOSS data[1 7 8]: Women from ethnic minorities (similar to non-pregnant adults among whom severe mental illness is also a risk factor[11]) and those with medical or mental health problems, or social complexity. These subgroups are common:

- Minority ethnic group women represent 14% of the UK population (2018 data), with a particularly high prevalence in London (40%).
- Co-morbidities complicate at least 20% of pregnancies, particularly obesity (≈20%), GDM (≈16%), asthma (up to 12%)[12 13], and hypertension (≈10%), with cardiac disease less common but particularly dangerous (≈2%)[14].
- 10-20% of women experience mild to severe perinatal mental health difficulties, and these often occur alongside physical problems among maternal deaths[14 15].

From the pandemic outset, the Royal College of Obstetricians and Gynaecologists (RCOG), Royal College of Midwives (RCM), Royal College of Paediatrics and Child Health, and the Obstetric Anaesthetists' Association have responded to government regulations and emerging experiences, by providing guidance for clinicians and policy-makers about delivery of the core NHS service of maternity care, despite anticipated staffing shortages, surges in critical care needs, and requirement to reduce face-to-face contact. The first edition of RCOG guidance was published on 9/Mar/2020 and the 13th iteration on 19/Feb/2021, with a 2nd version of guidance for maternal medicine services circulated on 19/Dec/2020. Service modifications have included: cancellation of perceived non-urgent activity; use of virtual care; out-of-office monitoring with rapid roll-out of digital resources to support remote care, combining appointments wherever possible; alternative screening pathways; and reduced choice of carer. More recently, College outputs have included a combined formal request to NHS Trusts and Boards to maintain maternity staffing levels, even during pandemic surges (18/Jan/2021)[16], maintenance of NICE-recommended schedules of antenatal and postnatal care; adequate staffing of day assessment and triage services, and encouragement of women to use them if they have concerns; choice for place of birth, including midwifery-led units and home birth; and advice about COVID-19 vaccination (see below).

Our national survey of maternity hospitals confirmed the extensive impact of the pandemic on UK maternity services[17], with the majority of units reporting: a reduction in antenatal

(70%) or postnatal appointments (56%), and emergent (unscheduled) antenatal presentations by women (89%); use of remote consultation (89%), particularly for antenatal booking and mostly via telephone rather than video; a change to screening pathways for GDM (70%); and temporary suspension of birth at home or in a midwife-led unit (59%). Also, many (40%) mental health care staff reported feeling less able to assess women, some of whom engaged poorly with virtual appointments, and there were particular challenges in assessing mothers' relationships with their babies[18]. Up to 80% of health visitors have been redeployed in some areas[19].

Our systematic review (39 studies) of pandemic-associated service reconfiguration was consistent our UK survey results. There has been a significant decrease in antenatal care attendances (clinic and unscheduled) and labour companionship, and an increase in virtual care and hospitalisations following unscheduled attendances[20]; 3/39 studies reporting UK clinical outcomes were consistent with findings overall, and adding reduced use of general anaesthesia for Caesarean or cervical cerclage, and higher demand for preterm birth clinic services[21 22].

Virtual maternity care

ALL pregnant women, and not just the 10% with COVID-19 infection, have been impacted by pandemic-necessitated service reconfiguration. For example, pregnancies may have been reduced in number by the inability of some women to have intrauterine contraceptive devices removed to plan pregnancy[23]. The 14% of heterosexual couples affected by infertility and seeking advice faced a temporarily suspension of services during the first wave of the pandemic, according to the General Direction 0014 given under the Human Fertilisation and Embryology (HFEA) Act, and changes in service delivery when restarted to minimise COVID infection, may have affected treatment effectiveness or safety. Some maternity units moved away, as recommended, from gold standard GDM screening practices in pregnancy (eg, oral glucose tolerance testing)[24], whereas others maintained pre-pandemic screening. Also, public health messaging to maintain social distancing and stay at home may have inadvertently affected women's care-seeking for problems in pregnancy[25]. There have been reports of more stillbirths and domestic violence[25 26], and there are many other unknowns.

Our systematic review (40 studies) has confirmed several changes in pregnancy outcomes in high-income countries during the pandemic (compared with before), including an increased odds of surgically-managed ectopic pregnancies (5.8-fold) and stillbirth (1.3-fold), reduced odds of preterm birth (by 9%), and poorer mental health outcomes (pooled mean difference in Edinburgh Postnatal Depression Scores of 0.42)[2]. The latter has been highlighted by the Mar/2021 rapid evidence review, 'Maternal mental health during a pandemic', Maternal Mental Health Alliance, UK report, and additionally, a cross-sectional survey of 614 UK mothers that documented high levels of depression (43%) and anxiety (61%), compared with historical levels[27].

Of 268 UK studies identified by literature review of virtual care and/or out-of-office monitoring on health care maternity costs, all studies assessed the impact of virtual care *with* out-of-office monitoring of BP or blood glucose (see below). None examined costs of virtual care as integrated into general maternity care that costs the NHS ≈£4.7 billion annually (2013/14)[28].

The views of healthy pregnant and postnatal women (46 studies) and those of health care-providers (17 studies) about routine antenatal care services (non-COVID-19) were summarised in a 2019 qualitative evidence synthesis[29] into three thematic domains: socio-cultural context, service design and provision, and the importance of personalised supportive care, information, and safety. Importantly, the first experience of women accessing antenatal care services shapes whether women continue to use these services. These themes were echoed in our semi-structured video interviews with 23 recently-pregnant participants, South London, whose pregnancies straddled pre-pandemic and pandemic epochs[30]. Template analysis themes were: (i) disruption to in-person care and increased virtual care provision; (ii) changes to labour and birth preferences and plans; and (iii) advice for navigating maternity services during a pandemic. Women reported mixed views on the reduction in

scheduled in-person appointments, a topic of parliamentary debate on maternal wellbeing (10/Mar/2021). The increase in remote care, especially via telephone and occurring postpartum, was not well-endorsed by these women, who reported under-reliance on health care professionals (vs. family and friends) for support. These themes are similar to those outlined in a realist synthesis (22 publications) of women with social risk factors (including ethnic minority membership); of particular relevance were: access to services (and interpreters), appropriate education, practical support (rather than just surveillance), continuity of carer, and a trusted care-provider to mitigate experience of discrimination and trauma[31]. We conducted similar semi-structured video interviews with 29 health care-providers from South London, with a focus on ethnic minority groups. The main theme was a health system under pressure, with tension between personal precarity ('keeping safe while fulfilling one's role') and changes to service delivery ('to build back the service').

Maternal out-of-office monitoring

Pre-pandemic, traditional care of pregnant women with hypertension and diabetes consisted of home BP monitoring (HBPM) by some hypertensive women and others at risk of developing hypertension, and routine capillary blood glucose monitoring in women with GDM. Out-of-office monitored values were usually brought to scheduled face-to-face antenatal appointments for review by care-providers, up to twice weekly at maternity clinics and day assessment units, particularly for hypertensive patients.

Even pre-pandemic, there was interest in out-of-office monitoring digital applications (apps) for two-way communication with care-providers, as an alternative to frequent outpatient appointments. HBPM may facilitate earlier detection and better control of pregnancy hypertension, while engaging women in care and reducing costs[32]. In our Nov/2018 systematic review of women with, or at risk of developing, pregnancy hypertension (11 studies, 725 women), antenatal HBPM was associated with fewer antenatal visits (by an average of 0.5 visits/woman) and antenatal hospital admissions (69% lower odds), less pre-eclampsia (50% lower odds), and fewer labour inductions (45% lower odds)[33]; there were no differences in maternal and fetal/newborn outcomes, postnatal readmissions, and costs were not reported. However, there was significant clinical heterogeneity and low quality of evidence. In our subsequent observational study (108 women) within the NHS, HBPM was associated with fewer outpatient attendances (by 0.8 attendances/week), regardless of the duration of monitoring, without an impact (favourable or unfavourable) on pregnancy outcomes[34], and with an average cost saving of £200/week[35]. Similar findings were reported in another small observational study that confirmed the acceptability of HBPM (75 women)[36]. Based on this promising observational work, the effectiveness of this approach was evaluated in the UK BUMP trials, due to report in 2021 (NCT03334149).

Use of out-of-office monitoring platforms for GDM were driven pre-pandemic by a rising prevalence and associated demand for clinical input. A GDM-specific app, GDm-Health, is NICE-approved for use in the NHS. GDm-Health is a monitoring and management system with blood glucose, meal, and medication upload to a clinician dashboard, allowing for the delivery of remote supervision. A 2020 systematic review and trial sequential analysis of telemedicine trials in GDM (32 trials, 5108 women) demonstrated a significant improvement in glycaemia and maternal/neonatal outcomes, with use of a variety of approaches, including health apps[37]; it was assumed that with improved outcomes, costs would be lower, but this was unsubstantiated by health economics data. A 2019 survey of 63 pregnant women with diabetes (including GDM) highlighted their frequent hospital visits, long waiting times in clinics, and willingness to self-manage and be monitored remotely by health care staff[38].

The pandemic accelerated use of HBPM and digital applications to facilitate virtual care, by sharing out-of-office BP and blood glucose values with hypertension and GDM care-providers. During the pandemic, unprecedented numbers of the ≈42,000 outpatient hypertensive pregnant women have been using HBPM to achieve social distancing and reduce visits. This approach was rapidly deployed, even by units unfamiliar with this technology. During the first wave of the pandemic, NHS England (NHSE) and NHS

Improvement purchased and distributed BP devices to facilitate remote monitoring. The RCOG published detailed advice on HBPM[32 34 35 39], including tools for units to manage distribution and return of BP measurement devices, actions for women based on BP values, and use of smartphone apps (like K2 Hampton and BPm-Health) to support communication between women and care providers[40]. For example, K2 Hampton use has increased from few Trusts pre-pandemic to 28 currently. Also during the pandemic, use of out-of-office GDM monitoring apps were incorporated into routine care for women previously considered to be ineligible for use of this technology, including those with language or other social challenges or type 2 diabetes; GDm-Health use has increased to 56 Trusts (from 16 pre-pandemic).

COVID-19 vaccination

COVID-19 vaccines available in the UK are all theoretically acceptable for use in pregnancy, as they do not contain live attenuated virus[41]. Based on vast prior experience with other vaccines in pregnancy and no hypothesised mechanisms for harm, similar efficacy and side effects are anticipated with COVID-19 vaccination in (vs. outside) pregnancy; however, pregnant and postpartum women were excluded from all vaccine trials globally until recently (see 'Ongoing research', below), and the precautionary principle requires '*evidence of no harm'* (rather than '*no evidence of harm*') before using an intervention in pregnancy.

Despite some public reservation, there is neither evidence that COVID-19 vaccination affects women's fertility nor a biologically plausible mechanism by which this may occur[42].

For COVID-19 vaccination in pregnancy, there have been no major safety signals from: animal reproductive toxicology studies; the very small number of inadvertent pregnancies in vaccine trials; the Center for Disease Control (CDC) V-safe post-vaccination health checker (with limited data on ≥30,000 pregnant women); or a formal pregnancy registry (>1800 enrolled to date)[43]. A recent report of American health workers who were pregnant (N=84) or lactating (N=31) when vaccinated, found that compared with non-pregnant controls (N=16), vaccine-induced humoral immunity was similar, antibody titres higher than following actual COVID-19 infection, and antibodies were present in umbilical cord blood and breastmilk, suggesting that vaccination can confer maternal and neonatal immunity[44].

In addition to safety concerns in pregnancy specifically, there is the consideration that vaccine acceptance is not uniform, and particularly low among ethnic minorities who are at heightened risk of severe COVID-19[45] but who may mistrust the medical community. In a recent survey of >1200 pregnant women, at least 2/3 would accept COVID-19 vaccination if offered, to protect themselves, their baby or loved ones, and others who are vulnerable (in equal measure); women who said that they would decline, cited concerns about potential fetal harm or otherwise insufficient safety data (presentation Chappell, 10/Mar/2021, Royal College of Physicians, online).

There is a lack of consensus about whether routine COVID-19 vaccination in pregnancy is appropriate. The UK Joint Committee on Vaccination and Immunisation advised (01/Mar/2021) that COVID-19 vaccines can be administered to women who are planning pregnancy (without delaying conception) or breastfeeding, but not routinely to pregnant women until more safety data are available. In contrast, the International Federation of Obstetrics and Gynaecology (FIGO), "…considers that there are no risks – actual or theoretical – that would outweigh the potential benefits of vaccination for pregnant women", and supports offering this vaccination to pregnant and breastfeeding women (02/Mar/2021). A merged information sheet from the UKTIS, RCOG, RCM, and MacDonald Obstetric Medicine Society (24/Mar/2021), highlights pregnancy groups at particular risk of severe COVID-19 who are currently offered COVID vaccination.

Ongoing research & what it will address

Much of the ongoing research within the NHS is focussed on COVID-19 infection and direct clinical sequelae in pregnancy, rather than the overall effect of the pandemic on maternity care[46]. Two pregnancy-focussed studies are evaluating the effects of suspected or confirmed COVID-19 infection (UKOSS; PAN-COVID), and a third, COVID-19 vaccination (see below). An additional 13 studies include (but are not limited to) pregnancy, and focus on

COVID-19 treatment. The national Maternity Services Data Set (MSDS) is due to report on the effects of the pandemic in England in Oct/2021; reports are usually published at this time for the prior financial year. However, 'submitters' vary widely, and most data relate to the delivery episode, excluding baseline body mass index (BMI, a key prognostic factor both in pregnancy and for COVID complications) and most processes of maternity care that should inform post-pandemic service planning (eg, virtual care).

Several ongoing projects focus on women's experiences during the pandemic, although none focus on those with lived experience of inequality. CORONET is using literature review and qualitative research to develop guidelines about what "good care looks like"; this will report in Aug/2021, but does not relate care to outcomes. Preliminary results suggest that virtual care is a poor fit for some women and continuity of carer has deteriorated[47]. ASPIRE builds on the international 'Babies Born Better survey', comparing the UK and Netherlands, and a mixed-methods 'snapshot' of maternity care and outcomes in eight Trusts only during the peak of the pandemic's second wave (Oct/20-Mar/21). Other projects include those focusing on women's mental health (PRAM, U Liverpool; RISEUP-PPD-COVID-19, NCT04595123) or specific adverse outcomes (eg, fetal/newborn loss [PUDDLES]).

A RCOG-led project is focused on inequalities and pregnancy outcomes (not experiences), using BadgerNet and K2 electronic maternity records. This will extend our understanding of the overall effects of the pandemic, but there will be less of the detail required for a deeper understanding of the relationship between outcomes and both individual-level characteristics (eg, co-morbidities) and processes of care (eg, virtual postnatal care).

The current COVID-19 vaccination research in pregnancy is focused on the implications of vaccination and some aims to link national routinely-collected UK data (eg, Hospital Episode Statistics, HES). However, these data are not available in the timely fashion required to detail pregnancy outcomes post-vaccination. Importantly, none of these studies will inform us about vaccine hesitancy amongst women who are planning pregnancy, pregnant, or postpartum, or the effectiveness of alternatives to vaccination. While pregnant/breastfeeding women were excluded from completed COVID-19 vaccination studies, two have just been launched and will have UK sites. These will study adverse events, pregnancy outcome, and maternal and neonatal serological response, in: (i) an open-label study (400 women) of the Janssen vaccine (NCT04765384); and (ii) a placebo-controlled trial (4000 women) of the Pfizer vaccine (NCT04754594). The UKOSS study has been extended to cover pregnancy outcome following vaccination. Also, there are three point-of care apps for COVID-19 vaccination details: Pinnacle, National Immunisation Vaccination System (NIVS), and National Immunisation Management System (NIMS)-1, all of which feed into NIMS and have (or will soon have) a pregnancy field. The UK Teratology Information Service (UKTIS) has been working with Public Health England (PHE) to link pregnancy vaccinations to pregnancy outcomes through national HES data. In addition, women can report vaccination to UKTIS by telephone and any adverse effects via the voluntary MHRA Coronavirus Yellow Card reporting site, and care-providers can report inadvertent vaccination to the PHE Inadvertent Vaccination In Pregnancy (VIP) site.

How this research will add to the body of knowledge

We know that the ≈10% of pregnant women infected with COVID-19 are at heightened risk of complications (whether symptomatic or not). 100% of pregnant and postpartum women have received modified maternity care services during the pandemic, but we do not know *how* service reconfiguration has affected outcomes (including costs) in the UK, and how to optimise care post-pandemic. Also, there is the new service of vaccination, our path out of the pandemic; whilst one in seven people in the UK are women of childbearing age (2019[48]), we have little data on use of COVID-19 vaccines in pregnancy planning, pregnancy, or breastfeeding, with no ongoing studies addressing their vaccine hesitancy, particularly as guidance for vaccination progress and data on vaccine efficacy and safety emerge[49].

3a. Why this research is needed now

Our dealings with COVID-19 are not over. New variants of the virus have emerged that are

more transmissible. Even when the pandemic is controlled in the UK, the country will still face threats from remaining areas of the world where it is not. There is also the potential that we will need long-term vaccination programmes.

The pandemic has forced NHS maternity services to undergo substantial pandemic-related change. While harms have been evident, there are also *potential* positives, such as: new ways of working may facilitate equity of access to care, better targeting of services (as for women with type 2 diabetes rather than GDM), cost reduction from health system and patient perspectives (virtual vs. face-to-face care), and acceptability. This is an opportunity to 'build back better' while there is political will for reform that is data-driven[50].

This project responds directly to the COVID-19 Marmot Review, and core themes of the Women's Health Strategy: Call for Evidence (8/Mar/2021), by investigating and responding to the impacts of COVID-19 on women's health, and by placing women's voices and priorities at the heart of research and improvement plans. This work will use clinical outcomes, women's preferences, and costs to inform post-pandemic health care to 'build back better'. This in line with UK Government's Long Term plan[51], and specifically, reduction of inequalities[52], promotion of the 'Better Births' agenda, halving of maternal and fetal/newborn deaths by 2030, and ensuring continuity of maternity carer, particularly for those who will benefit most. Our focus on vulnerable groups responds to the Maternal Mental Health Alliance's emphasis on understanding the longer-term emotional and psychological impacts of the pandemic, particularly among vulnerable groups of women. Our inclusion of costs ensures that digital options are not a way to save money at the expense of face-to-face consultations and therapies if more effective and/or preferred.

While the quantitative routinely-collected data (WP1) and qualitative interviews (WP2) will be from South London, this a socially and ethnically diverse population that is ideally placed to inform the national priority of inequality. Also, our real-time epidemiology about COVID vaccination (WP2) will recruit nationally through the established KCL-CSS/ZOE app, and WP3 will focus on four nation and UK-wide policy implications of WP1 and WP2 findings across the four nations, particularly with regards to inequalities.

4. AIMS & OBJECTIVES

In two Trusts providing maternity care in South London (Guy's and St. Thomas' NHS Foundation Trust, GSTT; and King's College Hospital NHS Foundation, KCH), we aim to study the impact on women and babies of COVID-19 pandemic-related maternity service configuration (i.e., virtual care, out-of-office monitoring, and vaccination), particularly those from minority ethnic groups or leading socially or medically complex lives.

We have **three objectives** to be addressed by quantitative, social science, and policy WPs:

(1) For all pregnancies, to study the impact on maternity care quality (effectiveness, safety, and acceptability), maternal and offspring outcomes, and costs within the context of: maternity care service configurations, particularly: virtual consultations; out-of-office monitoring (eg, patient reported BP); and COVID-19 vaccination (ie, provision, uptake, and adverse events).

(2) Explore and describe the perceptions and experiences of pregnant and postpartum women during the pandemic, with a focus on those who: identify with an ethnic minority group; have medical or mental health co-morbidities; and/or live with social complexity, including socioeconomic deprivation.

(3) Across the four nations, engage with stakeholders to develop policy interventions for local, regional, and national health systems.

5. RESEARCH PLAN/METHODS

Our objectives will be addressed by asking the following specific questions, organised in Table 1 by aspect of service configuration examined and WP methodology (next page).

Table 1: Research questions according to service configuration and WP1 and WP2*

Types of service reconfigurations		WP1 (quantitative)	WP2 (social scienceł)
Virtual care	**Cross-cutting**: Maternity care for ethnic minority women or those living with social or medical complexity		
ANC booking frequency & impact on:			
Timeliness		eLIXIR‡	IDIs
Identification of risk factors for adverse outcome		eLIXIR‡	
Implementation of associated care pathways (eg, GDM risk identification and screening by OGTT)		eLIXIR‡	IDIs
Prescription of preventative care (eg, aspirin for pre-eclampsia prevention, thromboprophylaxis)		eLIXIR‡	IDIs
Receipt of fertility services, associated COVID-19 infection, complications, livebirths/other outcome		eLIXIR‡, HFEA	IDIs
Pregnancy and mental health outcomes		eLIXIR‡	IDIs
Post-booking ANC contact frequency & impact on:			
Screening for pregnancy hypertension (N appts per woman with BP recorded)		eLIXIR‡	
Continuity of carer		eLIXIR‡	IDIs
Unscheduled visits (eg, Medical Assessment Unit)		eLIXIR‡	IDIs
Intended and actual place of birth		eLIXIR‡	
Pregnancy and mental health outcomes		eLIXIR‡	
Workforce demands		-	- (HCPs*)
Patient experience		-	- (women*)
Postnatal care			
Breastfeeding		eLIXIR‡	IDIs
Readmission (maternal or newborn)		eLIXIR‡	-
Cost		eLIXIR‡	-
Rapid implementation of out-of-office monitoring			
Hyperglycaemia in pregnancy			
Use of GDm-Health app and use as advised		GDm-Health	IDIs
Glycaemic control (in-range readings, mean out-of-office monitored values based on those in app, and laboratory measures)		eLIXIR‡, GDm-Health	IDIs
Management of glycaemia (i.e., diet only, oral hypoglycaemia therapy and/or insulin)		eLIXIR‡, GDm-Health	IDIs
Health care utilisation (ie, ANC contacts - virtual or face-to-face and scheduled or unscheduled)		eLIXIR‡	IDIs
Workforce demands		eLIXIR‡	- (HCPs)
Pregnancy and mental health outcomes		eLIXIR‡	IDIs
Cost		eLIXIR‡	-
Pregnancy hypertension			
Use of BPm-Health as advised		BPm-Health	
BP control associated with maternal out-of-office monitoring (in-range BP, severe hypertension, mean out-of-office BP from app)		eLIXIR‡, BPm-Health	-
Antihypertensive therapy use		eLIXIR‡	-
Pregnancy & mental health outcomes		eLIXIR‡	IDIs
Cost		eLIXIR‡	-
COVID-19 vaccination in planning pregnancy, pregnancy, and postpartum			
Uptake of vaccine when offered		eLIXIR‡	IDIs, KCL-CSS/ZOE app

Types of service reconfigurations		WP1 (quantitative)	WP2 (social science†)
Adverse effects		-	KCL-CSS/ZOE app
Pregnancy and mental health outcomes		eLIXIR‡	IDIs, KCL-CSS/ZOE app
ANC (antenatal care), BP (blood pressure), eLIXIR (early-LIfe data cross-LInkage in Research), GDM (gestational diabetes mellitus), GSTT (Guy's and St. Thomas' NHS Foundation Trust), HCP (health care-provider), IDI (in-depth interview), KCH (King's College Hospital NHS Foundation Trust), KCL (King's College London), OGTT (oral glucose tolerance test) ** Social complexity is: experiencing domestic violence, homelessness, living within the travelling community, substance/alcohol abuse, seeking asylum or refugee status, learning or physical disabilities, safeguarding issues, or mental health issues[53 54]. Medical complexity is: one/more pre-existing or pregnancy-induced conditions.* *† IDIs with women - only ethnic minority women or those living with social or medical complexity.* *‡ eLIXIR has linked data from two South London maternity Trusts (GSTT, KCH), one mental health Trust (Maudsley). Consent covers future linkages with NHS Digital data, subject to ethics amendment.*			

WP1 (Magee, Lead): QUANTITATIVE methods to describe, quantify and explain using routinely-collected, linked maternity and offspring data

The MRC-funded eLIXIR platform was established in Oct 2018 as a unique population-based prospective cohort of maternity, newborn, and mental health records from two NHS Trusts providing maternity and newborn care (GSTT and KCH which covers the Denmark Hill and Princess Royal University Hospital sites), and one mental health NHS care-provider (South London and Maudsley, SLaM), with associated linkages with community (Lambeth DataNet, LDN) and HES[55]. Data are available for ≈14,000 births/year.

As in the Flow Diagram (Upload), maternal and offspring data ('clinical dataset') are downloaded from maternity and neonatal electronic health records at GSTT and KCH ('clinical data source'), and transferred to the SLaM Clinical Data Linkage Service (CDLS) safe haven, run by the Clinical Record Interactive Service (CRIS), SLaM, a trusted third-party service since 2007-8, with robust data security and governance procedures. The clinical dataset is structured, linked with other datasets (as relevant), de-identified, and transferred to the eLIXIR data warehouse, all within the safe haven. For projects approved by the eLIXIR Oversight Committee (as for this proposal), there is controlled user access to de-identifed data for extraction, cleaning, and analysis, all behind the SLaM firewall.

The Trusts contributing data to eLIXIR serve a diverse population, with a mix of deprivation and affluence similar to the London average; Lambeth and Southwark are the 29th and 40th most deprived local authorities in England, and Bromley is 208th of 317. Just over half of the women were born outside the UK, and 30% do not speak English as their first language[55]. One in five local residents lives with multimorbidity, particularly anxiety and depression among those of reproductive age[56]. Given these Trusts' specialist services, the population is enriched by women with severe, multiple, and/or complex health issues, identified nationally as increasing in number given secular trends in non-communicable diseases, and contributing to 90% of maternal deaths[14]. Established UK definitions of ethnic minority groups[57] and social complexity[53 54] are defined in Table 1 footnotes.

Pregnancy and childbirth data in eLIXIR are based on the NHS-approved and cloud-based Clevermed BadgerNet system. BadgerNet Maternity is used in >40 UK units, and BadgerNet Neonatal in all UK neonatal care units. However, studies undertaken using eLIXIR data have the potential to influence maternity nationally. Replication of eLIXIR data linkage offers the potential to develop a national data network for additional statistical power and cross-site comparisons; see Section 10, Collaborator Reynolds, PI of 'Born in Scotland'.

eLIXIR data will be linked with emerging data from out-of-office monitoring, HFEA for infertility treatment, and NIMS for vaccination – all new 'clinical datasets' to be linked with eLIXIR data within the SLaM CDLS safe haven (Flow Diagram). These linkages are enabled by women's 'opt-out' consent, according to Section 251, for use of data to understand the impact of maternity care on maternal and child outcomes. The linkages are 'living', meaning that they can be refreshed as the cohort grows, providing a unique data asset for our work.

Pregnancy outcomes will be linked to the BP and blood glucose data from the Sensyne Health apps. The GDm-Health app and online platform is NHS-recommended. Use was selective for GDM at GSTT and KCH from mid-late 2019, and uniform for women with GDM or type 2 diabetes during the pandemic, regardless of language skills or perceived ability, to deliver the mandated virtual care consistent with NICE guidance. While initial feedback was positive, this care pathway must be evaluated, with regards to glycaemic control, pregnancy outcomes, costs, and acceptability (women and care-providers). The BPmHealth app was launched during the pandemic, in line with RCOG guidance and NHSE's investment in BP devices for out-of-office BP monitoring during the pandemic[58]. The app is based on that used in the BUMP2 out-of-office BP monitoring trial[32]; the results due in 2021 will inform BP targets from NICE 2010 (<150/100mmHg) rather than 2019 (≤135/85mmHg)[59].

Currently, there is no national-level mechanism able to assess the volume and depth of data necessary to understand not just trends in outcomes, but what underlies them, and in a timely fashion. The MSDS is a national-level extract from local maternity records that is working towards this and is currently used as the basis of the large-scale National Maternity and Perinatal Audit (NMPA) of NHS maternity services across England, Scotland and Wales and run by the RCOG (Khalil, Obstetric Lead). However, data quality has been challenged by incompleteness, a limited number of variables, and a lack of timeliness (reflecting care delivered at least one year prior), making it unsuitable for the work we propose. While NHSE has added specific data points to capture social complexity and quality of care (eg, continuity of carer), and is working to improve standardisation and semantic interoperability through the Information Standard and introduction of Systematized NOmenclature of MEDicine Clinical Terms[60], eLIXIR provides greater granularity than MSDS that will enable understanding the complex changes that occurred during the pandemic and exploration of inequalities.

Analyses will be objective-specific and address questions in Table 1. We will describe and quantify population-level temporal trends in maternal and offspring health outcomes and costs, between pre-pandemic (01/Oct/2018 to 28/Feb/2020), pandemic (01/Mar/2020 to 30/Jun/2021), and post-pandemic epochs (01/Jul/2021-to be confirmed), and according to possible booking and delivery within or bridging each epoch. Inequalities will be described across minority ethnic groups, social complexity, and complex condition groups. Descriptive statistics will present measures of central tendency, variation, and temporal trends to characterise maternal and fetal/newborn outcomes over time. Peaks and troughs of health care outcomes and costs across the maternity pathway will be identified, along with population groups with particularly high needs before, during, and after the pandemic.

To formally test the impact of the pandemic on pregnancy outcomes and costs, we will undertake an interrupted time-series (segmented regression) analysis[61 62] with Newey-West standard errors[63]. Autocorrelation and seasonality (eg, periodic changes in health care utilisation underlying maternity costs) will be assessed by inspecting the autocorrelation and partial autocorrelation functions. Statistically significant changes in level and/or trend in average health outcomes and costs since the pandemic started will be assessed. Sensitivity analyses will: (i) exclude the small number of women with confirmed COVID-19; and (ii) examine the sensitivity of results to alternative pandemic timing definitions; and (iii) examine a simplified interrupted time-series design (ie, 'bent-stick' rather than 'broken-stick') if there are limited numbers of women for a particular analysis.

To assess effects of virtual care, out-of-office monitoring apps, and COVID-19 vaccination on health outcomes and costs, individual-level multivariate regression models will be calibrated. A separate model will be estimated for each outcome and service reconfiguration

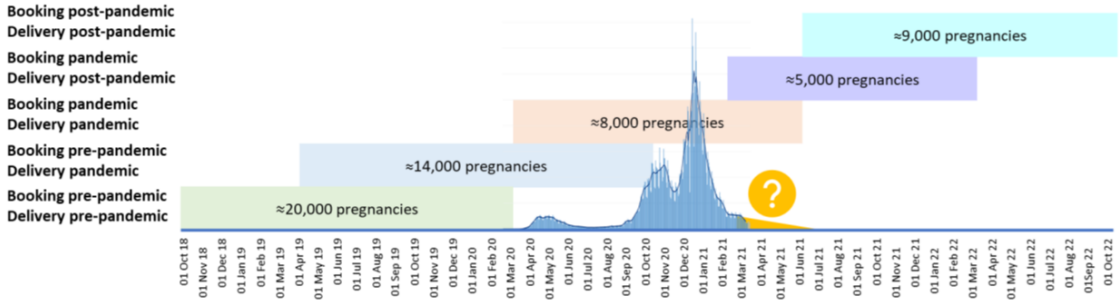
(ie, virtual care, out-of-office monitoring, or COVID-19 vaccination). Models will control for an 'intervention' variable (indicating virtual care receipt, out-of-office monitoring app use, or COVID-19 vaccination receipt). COVID-19 diagnosis, percentage time of pregnancy during the pandemic, and sociodemographic factors[64]. P<0.05 will be considered statistically significant for individual outcomes, but we seek as meaningful a coherent pattern of related results to be interpreted in light of WP2 findings.

We will capitalise on eLIXIR data linkage of maternity data with LDN and HES, to build comprehensive mother-newborn costs, from a NHS perspective, from antenatal care booking until 6 weeks postpartum. Maternal and offspring costs will account for antenatal (hospital or health centre midwife or obstetrician-led antenatal appointments, attendances to day assessment units, antenatal inpatient admissions), intrapartum (inpatient admission), and postnatal/neonatal activity (maternal stay in postnatal ward, high-dependency unit, neonatal intensive care unit)[65]; General Practice consultations, Accident and Emergency visits, psychological therapy through Improving Access to Psychological Therapy, and medications will also be included. Service utilisation will be valued based on national unit costs for maternity and health care services from NHS reference costs 2015-16, Unit Costs of Health and Social Care 2020, Clinical Negligence Scheme for Trust contributions per staff member, and the British National Formulary. All unit costs will be presented in pounds sterling (£), for base cost year 2020/21, and adjusted for inflation (Hospital and Community Health Services pay and price index). For out-of-office monitoring app users, costs will also include health care-provider interactions through the app, including scheduled (virtual) and patient-initiated appointments (eg, call-back request, such as when glucose levels have been uploaded and advice is requested), and care-provider-initiated messaging (eg, abnormal uploaded glucose levels require discussion). Quantitative information will be supplemented by qualitative collected in IDIs with health care-providers (WP2).

For each service reconfiguration, costs and health outcomes effects will be juxtaposed in cost-consequence analyses. Resource use, costs, and selected effectiveness outcomes will be presented separately, in disaggregated form. Effectiveness will be measured through a range of outcomes, such as spontaneous preterm births, hospital re-admissions, and mental health (eg, Whooley depression screen, and treatment in secondary mental health services, antenatally and postnatally in the first three months). Analyses will adhere to good practice guidelines[66] and NICE public health reference case. Subgroup analyses of maternal and offspring costs and effectiveness by ethnicity, so-cial complexity, and complex conditions will be conducted assuming sufficient sample size.

Ours is a convenience sample of available eLIXIR data, covering each of pre-pandemic (01 Oct 2018-28 Feb 2020, ≈20,000 births), pandemic (≈14,000 births), and post-pandemic (to be determined) care epochs (Fig 2). With alpha of 0.05 and power of at least 80%, the large sample size will be sufficient to detect clinically important changes from baseline[55] in key outcomes other than perinatal mortality, such as a 10% relative risk reduction in spontaneous preterm birth from 8.6% to 7.7%, or detect a 20% (±2%) difference in COVID-19 vaccination uptake between White and minority ethnic group women, a difference similar by ethnicity outside pregnancy (and based on uptake of 70% and 50%, respectively).

Fig 2: Antenatal care booking and deliveries available in eLIXIR, according to pre-pandemic, pandemic and post-pandemic epochs (the latter yet to be defined, as shown by '?')



WP2 (Silverio, Easter, Duncan, co-Leads): SOCIAL SCIENCE to enrich understanding

In-depth interviews

We will undertake 105 IDIs with a maximum diversity sample of pregnant women (n=40; 25 national, 15 local), partners (n=15; 10 national, 5 local), health care-providers (n=25; 15 national, 10 local), and policy-makers (n=25; 20 national, 5 local) with lived experience of receiving or providing mater-nity services during the pandemic (Flow Diagram, Upload). We will recruit locally and nationally, online (through social media and websites) and through existing and new collaborations, sign-positing to relevant charities, groups, and organisations, so that we can target women who undertook out-of-office monitoring (ie, hypertension or GDM) and those with complex health problems (eg, GDM or obesity), as well as associated care-providers (including midwives, obstetricians, physicians, specialist nurses, anaesthetists, GPs, and health visitors), and policy-makers (including senior management and regional representatives, from Local Maternity Systems and Heads of Midwifery).

The interview schedule will be adapted to complement evolving knowledge, and explore with interviewees what changed in care, what it meant to them, and whether they were confident about the care received/provided or offered (for COVID vaccination), as appropriate. We are particularly interested in quality of care. For virtual care, this will focus on: identification of risk factors and implementation of appropriate care pathways at antenatal care booking; continuity of carer and unscheduled visits for ongoing antenatal care; and newborn care for postnatal services. For out-of-office monitoring, our interests will focus on women's self-efficacy, especially given reductions in face-to-face contacts and expansion of use to women who would not have previously used the app, and staff confidence. For COVID-19 vaccination, this will focus on vaccine uptake and rationale (including whether these views were preformed or related to experiences of care), during pregnancy and breastfeeding, as well as risk communication. Across the three sections, we will explore the impact of the service configuration on inequalities.

Videoconferencing will be used to conduct and record interviews, with face-to-face interviews in South London or telephone nationally offered as alternatives. Recordings will be encrypted for cloud storage and transcribed. Analysis will be undertaken using thematic framework analysis for cross-disciplinary health research[67], with the groups together (for breadth and interaction) or separately (for depth of individual experiences or to study group-specific regional differences), depending on the research question being addressed.

We will complement information the IDIs with site-level feedback, such as through the maternity experiences survey, and mapping of pandemic-related policy and health system changes and innovations across KHP, using operational and policy document text reviews. We will use a framework adapted from Kruk[68], Hanefeld[69], and the World Health Organization[70], to understand how our regional health system has responded to the pandemic and guide recommendations for rebuilding a resilient maternal health system[71]. By collecting qualitative data from four groups (women, partners, health care-providers, and policy-makers), we will be able to stratify and compare data by participant type, using NVivo Qualitative Data Analysis software, to identify similarities and differences.

Real time epidemiology

Questionnaires will be administered to maternity service users nationally (≈43,000) via the KCL-CSS/ZOE app, enabling participation in the CSS Biobank, to gather data about vaccine uptake, hesitancy and side effects.

The KCL-CSS/ZOE app, recruiting citizen-scientists through mobile technology, was launched jointly by ZOE Global Ltd. and KCL researchers on 24/Mar/2020, with researchers from the Massachusetts General Hospital (MGH) and Lund and Uppsala Universities[72]. Over 4.5 million KCL-CSS/ZOE users are in the UK.

KCL-CSS/ZOE app data have contributed greatly to: understanding of COVID-19, its impact on people's lives, and health care policy, nationally and internationally. There have been >40 high-impact publications to date, including those on pregnancy[6], racial and ethnic differences in COVID-19 vaccine hesitancy and uptake, vaccination after-effects and subsequent

COVID-19 infection, and attributes and predictors of Long COVID[45 73 74]. Researchers at KCL have evolved a close working relationship with the government's Scientific Advisory Group Executive, NHS teams, and infectious disease epidemiologists to tackle the country's challenges during the pandemic, the latest of which is vaccination.

In brief, after KCL-CSS/ZOE app download, participants are asked to provide basic demographic information, including age, sex, ethnicity (self-identified based on standardised categories from the Office for National Statistics, UK[57]), education and income (based on English Indices of Deprivation 2019, IMD), frontline health care worker occupation, BMI, co-morbidities, smoking status, and prior COVID-19 infection[75]. Invitations have been issued to individual app users regarding interest in individual studies (eg, nutrition or mental health).

Two days after the first authorised vaccine was administered to the public (10/Dec/2020), the KCL-CSS/ZOE app was updated to include questions about whether UK participants had received vaccination, and if so, which vaccine (if known), with similar questions in place for the second dose. On 7/Jan/2021, a question was added about vaccine hesitancy, and the underlying reasons (as applicable), and any suspected vaccine-related symptoms for those accepting the vaccine. In this way, the app is helping to monitor, overall and by region, vaccination roll-out, including uptake and associated barriers, short-term side effects not serious enough to generate a response through the 'Yellow Card' reporting system (see Section 3, 'Ongoing research'); potential rare effects; and impacts on longer-term health.

While pregnancy was initially included in baseline questions during the early first wave of the pandemic, status was asked only at app enrolment, so the KCL-CSS/ZOE app no longer has valid information about who is currently pregnant. Questions about breastfeeding and pregnancy planning have been included only as reasons for vaccine hesitancy; there is no further information, so women could be planning pregnancy, pregnant, or breastfeeding, and specific concerns that could identify modifiable barriers cannot be explored.

As in the Flow Diagram (Upload), we will provide the KCL-CSS/ZOE app team with our selection criteria for app users (ie, women of reproductive age) and invitation requirements (wording). Invitations will be emailed to those users to join a study about COVID vaccination for women who are planning pregnancy, pregnant, or postpartum (within one year, whether or breastfeeding or not). We will indicate our particular interest in hearing from minority ethnic group women and those 'living in difficulty'. Invitations will be individualised. Potential participants will accept by clicking a link that will take them to the CSS Biobank website, KCL. Although the CSS Biobank was designed to enable studies of Long COVID (and biological sampling), this is not a requisite component, and recruitment can be adapted for other purposes, with ethics in place for invitations via the KCL-CSS/ZOE app, for initial recruitment and recontact.

Within the CSS Biobank, following consent, women will be asked for details of their pregnancy planning, pregnancy, or postpartum course, as relevant, in addition to essential worker status other than health care. This will include due date to facilitate follow-up. Similar to the KCL-CSS/ZOE app questions, women will be asked about their intent regarding vaccine uptake (and underlying reasons, adding exploratory questions regarding concerns for the baby or other children), whether or not they have been vaccinated (and details) and if so, any side effects (including injection site reactions). Effectiveness (compared with other preventative measures, such as handwashing, physical distancing, and mask-wearing) will also be assessed, with questions about other symptoms, any testing for COVID-19, mental health, and parent-infant bonding and results. Six weeks after the specified due date, users will receive a request for basic pregnancy outcome data, including complications.

Analysis: Descriptive statistics will be presented for our study population (of pregnancy planning, pregnant, and postpartum women) and other women of reproductive age, for baseline characteristics, vaccine uptake (initially and over time), reasons for vaccine hesitancy, injection site symptoms (as relevant), local and systemic reactions, subsequent COVID (ascertained through ongoing KCL-CSS/ZOE app use), and pregnancy outcome.

We will use multivariable logistic regression to compare COVID-19 vaccine hesitancy,

vaccination side effects, vaccination-era COVID infection, and pregnancy outcomes for our population of interest (compared with women of reproductive age), adjusted for age, ethnicity, social deprivation centile, frontline health care worker, BMI, co-morbidity (ie, one/more of diabetes, mental health problems, heart disease, lung disease, kidney disease, or cancer), current/prior smoking status, prior history of COVID-19 infection, essential worker occupation, and date of study entry. Effect estimates will be expressed as odds ratios (OR) and 95% confidence intervals (CIs). Analyses will be performed using Python (version 3.8).

Sample size: In our pregnancy symptoms study to 7/Jun/2020[6], there were 1,170,315 KCL-CSS/ZOE app users, aged 18-44 years with known pregnancy status, of whom 14,049 (1.2%) were pregnant. UK KCL-CSS/ZOE app use remains high (>4.5 million). Based on the following assumptions, we anticipate a sample size of ≈43,000 women over the two years: ≈14,000 app users who are pregnant/year and a similar number (≈14,000) who are postpartum or breastfeeding, ≈11,000 planning pregnancy (given planning rates of 50% and an additional ≈4000 women [1 in 7 couples with subfertility[76]]), and 55% participation in the CSS Biobank based on prior targeted invitations to KCL-CSS/ZOE app users.

WP3 (Nelson, Lead): STAKEHOLDER ENGAGEMENT within local, regional, and national maternity systems, to identify lessons learnt, high-impact actions and illustrative case studies, through regional listening event and a national Policy Lab.

These events are designed to maximise the impact of the research findings ('*what was and what is*') on evidence-informed policy-making and clinical practice, by bridging the gap between research evidence, policy, and practice change. The events will: bring together research, policy and practitioner expertise, respectful of our particular interest in disparities; use traditional and innovative engagement mechanisms; and be respectful of wider social and financial implications of policy options[77].

Regional listening events ('imagining our best future')

These are planned in each UK nation (in Cardiff, Belfast, Glasgow, and Birmingham) to assess WP1 and WP2 evidence, and complementary evidence, using an adapted framework[68-70], to guide discussions about local/regional governance, financing, technology, analytics, resources, and services, and explore:

- What worked and should be retained, or did not work and should be reversed;
- Brainstorm, shortlist, and prioritise high-impact future actions; and
- Understand facilitators and barriers to action implementation.

National Policy Lab ('co-production for action')

This will explore listening event findings and co-produce an 'imagine our best future' report for stakeholder consultation and dissemination. This report will be a visually-appealing and easy-to-read policy brief focussed on our most important findings of relevance to policy-makers, and maximise our impact on policy and care. For example, The Policy Institute's brief from work with the Mental Health and Justice research team, informed independent review of the Mental Health Act and reviewers' recommendations to the Prime Minister.

Also, co-production with women and health care-providers will include tools (eg, for virtual care), infographics, reports, presentations, Policy Institute's blog, and publications, to disseminate our findings to the NHS, local authority operational networks, and policy research channels.

6. DISSEMINATION, OUTPUTS & ANTICIPATED IMPACT

Our strategy will include engagement events across the four nations; virtual engagement via webinars, online platforms, and social media; publication of a plain-language and scientific website and report; and conventional academic outputs, such as presentations at premier perinatal and midwifery national and international conferences, and publications in high-impact, peer-reviewed, open-access journals. Joint press releases will be co-ordinated by the KCL press office with NIHR, participant universities, and collaborating Trusts.

We will disseminate our findings through an established network of local, regional, and

national stakeholders. Many of the co-applicants sit on relevant guideline and (national and international) stakeholder committees, including user groups, and will disseminate the findings via this involvement. We will work with national leaders in professional organisations (eg, RCM, RCOG), charities (eg, Tommy's, Sands, Birthrights, Fertility Network UK, National Childbirth Trust, Local Maternity Voices Partnership) to target midwifery and lay audiences through specific fora and relevant websites.

Our impact will be broad, on:

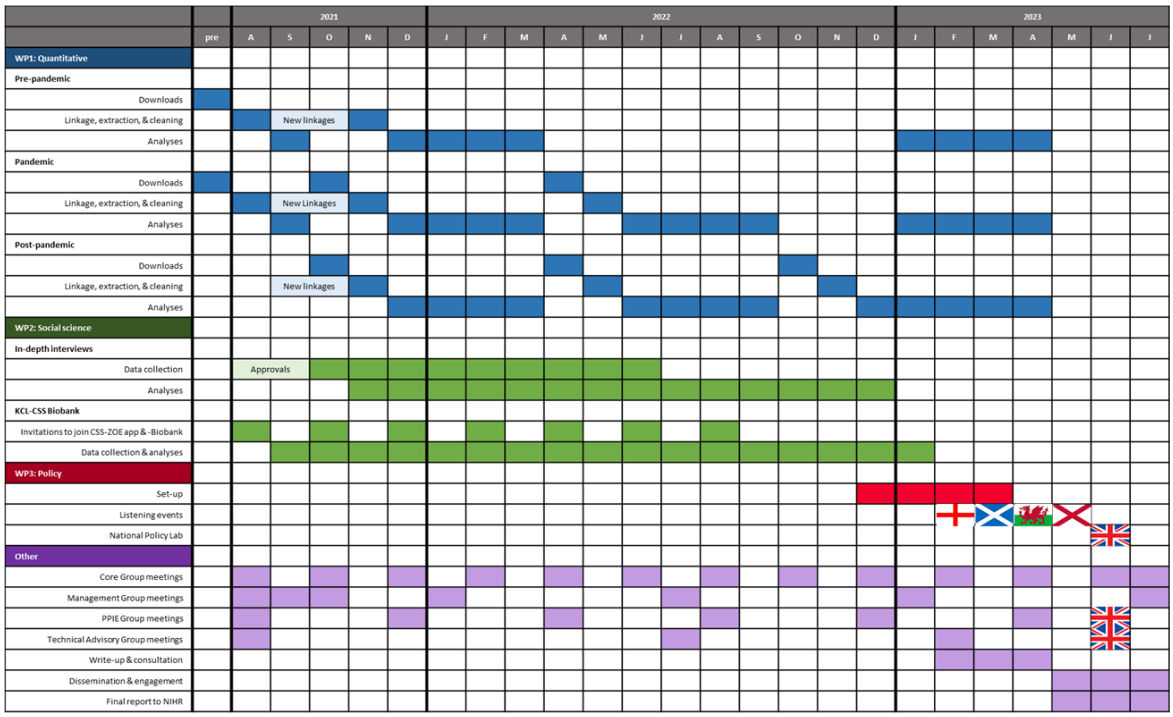
● Individual patients: improved care quality (effectiveness, safety, experience) and decision-making for >600,000 UK pregnancies/year and at least as many women planning;
● NHS maternity providers: strengthened evidence to inform service reconfiguration and support vaccination role-out;
● NHS Long Term Plan: maternal and fetal/newborn death and morbidity addressed and implementation of digitally-enabled care supported;
● Wider society: innovation to commercialise and decrease direct and indirect societal costs.

We anticipate receptiveness to the results given this unique opportunity that the health care system has to change, and the reality that COVID is likely to be with us in some form for the foreseeable future. The project has strategic alignment with the: (i) NHS; (ii) Maternity Transformation Programme and NHSE/Improvement; (iii) Institute of Women and Children's Health (IWCH), King's College London (KCL) to be a strategy delivery vehicle for learning from routinely-collected data into daily practice; (iv) Tommy's National Centre for Maternity Improvement to support use of data for health care improvement; (v) Diabetes UK through the RCOG Maternal Medicine Clinical Study Group (LAM, Chair); and (vi) MBRRACE (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK).

The approaches taken in this proposal (ie, eLIXIR and KCL-CSS/ZOE app and CSS Biobank) leverage unique data assets. Through linkages with primary care in eLIXIR (ie, LDN) or ongoing contact through the CSS Biobank, there is potential for further follow-up of women and babies should signals warrant (eg, Long COVID for mothers or neurodevelop-mental problems for babies given this virus' neurotropism) or other pregnancy complications (such as heightened cardiovascular risk following pregnancy hypertension or GDM).

7. PROJECT/RESEARCH TIMETABLE

Fig 3 presents the timelines, for this 24-month project by WP



WP1 (in **blue**, Fig 3): As described in Section 5, maternal and offspring data for eLIXIR are downloaded from BadgerNet Maternity and Neonatal records at GSTT and KCH every Apr and Oct. Data are transferred to the CDLS and linked with other partner datasets, ready for extraction, cleaning, and analysis for specific projects. As such, all data from the beginning of eLIXIR (01/Oct/2018) will have been downloaded up to and including Apr/2021, and available (and approved) for use at project commencement. New linkages (eg, HFEA) will require an ethics amendment, anticipated to take up to two months and so relevant from the Oct/2021 download. Fig 3 describes data downloads until Oct/2022, to gather as much data as possible about women who book (from Jul/2021) and deliver (from Dec/2021) post-pandemic in the new maternity system *status quo* that, at the time of grant submission, has yet to be achieved. If another wave of the pandemic occurs, we could undertake an Apr/2023 download.

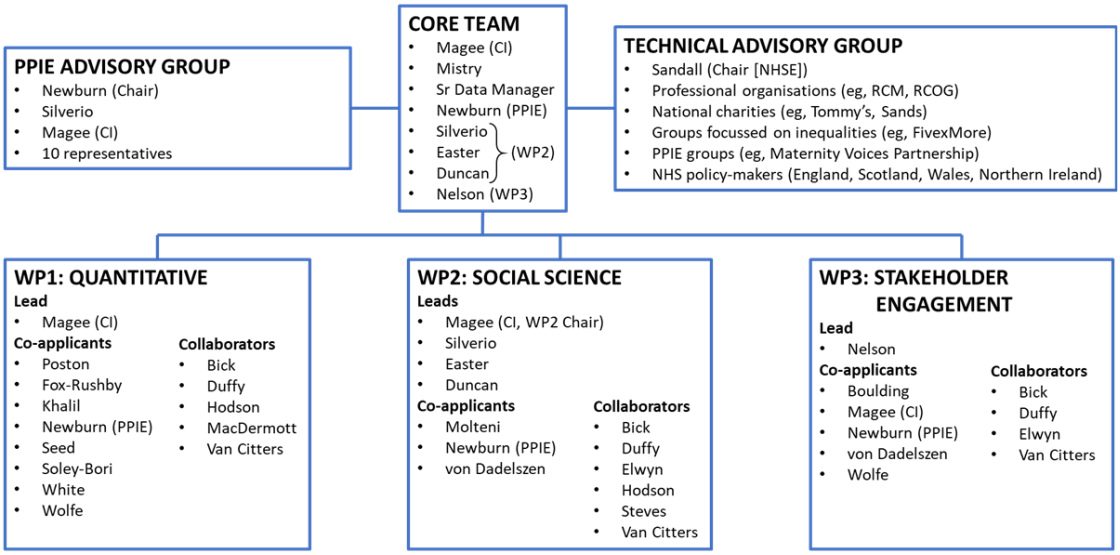
WP2 (in **green**, Fig 3): IDIs will be completed in 2022, following ethics approval (months 1&2), data collection (months 2-11), and analysis and write-up (months 4-17). The CSS Biobank vaccination study will commence immediately with recruitment of women of reproductive age who are KCL-CSS/ZOE app users (alternate months until Apr/2022), eQuestionnaire completion through the CSS Biobank and analysis (months 2-18).

WP3 (in **red**, Fig 3): Set-up (months 17-20) will be for regional listening events (months 19-22) and national Policy Lab (month 23).

Project management (in purple, Fig 3) is discussed in Section 8, below.

8. PROJECT MANAGEMENT

Magee (CI) will be responsible for distribution of funds, progress and timely study completion. (For team expertise, see Section 10. For details of specific roles, see 'Lead Applicant Role' [Magee] and 'Justification of Budget' [co-Is].) **Fig 4** shows our organisation chart.



Our **PPIE Advisory Group** will meet every four months, and consist of Newborn (PPIE Lead), Silverio (qualitative), Magee (CI), and ten individuals from South London, with representation from minority ethnic group women and those living with social/medical complexity.

The **Core Team** will meet alternate monthly, and consist of the Magee (CI), Mistry (Project manager); Senior Data Manager, Newburn (PPIE); and the WP leads. This group will review study progress, problem-solve around any barriers, review results, and plan dissemination.

Each **WP team** will meet every one to two weeks, joined by Magee (CI), Mistry (Project manager), and Senior Data Manager to provide close oversight.

The **Management Group** (core team, co-applicants and key collaborators) will meet monthly initially (virtually), and then at 6, 12, 18, and 24 months, for a half-day (face-to-face).

Our **Technical Advisory Group** will have a national focus and meet with the core team

three times (months 1, 12, 18). Professor Jane Sandall has agreed to chair, in her role as Inaugural Head of Midwifery Research, NHSE, and given her particular expertise in inequalities and policy. Members will be independent, and invited based on their varied perspectives, from: professional organisations (eg, RCM, RCOG), charities with national reach (eg, Birthrights, Sands); groups focussed on inequalities (FivexMore); a bespoke Midwifery Stakeholder Reference Group; PPIE groups (eg, Maternity Voices Partnership); NHS policy-makers across the four nations. Letters of support for the project from potential TAG members are available here – Sands, Birthrights, and Maternity Voices Partnership.

As this is not an intervention study, there will be no Data Monitoring Committee.

9. ETHICS/REGULATORY APPROVALS

Regarding the eLIXIR data, opt-out information and details of the project are given to each patient entering maternity and neonatal services, and patients have the option of opting out of the programme at any time. Approval under this legal framework was granted by the Health Research Authority (HRA) Confidentiality Advisory Group (CAG) to the eLIXIR team for existing linkages (ie, BadgerNet Maternity and Neonatal, SLaM for mental health services, LDN, and HES), which allow data to be available in an identifiable format to a small number of data-processing staff in accordance with data sharing contracts between the data provider institutions (HRA CAG Ref: 18/CAG/0040). Planned linkages within eLIXIR (for comprehensive GDm- and BPm-Health apps, HFEA, and NIMS) require an amendment to the ethical and Section 251 approval (of the NHS Act 2006 which allows the common law duty of confidentiality to be set aside where 'opt-in' patient consent is not practical).

eLIXIR data are managed by and stored at the CDLS at SLaM (Oxford C REC 18/SC/0086, Cambridge East REC 18/EE/0120). As the data processor for eLIXIR, the CDLS is a trusted third-party service, providing researchers access to linked clinical data in accordance with the strict governance conditions and processes agreed with relevant data controllers. The CDLS is managed by a small, dedicated team of informaticians, information technology and governance professionals, and currently hosts a range of datasets already linked with the SLaM CRIS mental health case register. The CDLS co-ordinates secure data transfer and facilitates data linkages within the CDLS safe haven (as for our planned new linkages). There is no direct access by researchers to the full linked eLIXIR data files which enhances data protection and confidentiality. CDLS is responsible for secure store of linked data, in accordance with predefined information governance and security standards. CDLS prepares data extracts for defined projects, as approved by the Oversight Committee (DL009).

The KCL-CSS/ZOE app research was approved by the MGH Human Research Committee (Ref 2020P000909) and KCL Ethics Committee (Ref 18210).

The investigators will ensure that research in this proposal is conducted in line with Good Clinical Practice Guidelines. Work not already covered by existing approvals will start only after gaining appropriate ethics approval, once we are informed of a successful outcome of this grant application.

10. PROJECT/RESEARCH EXPERTISE

Professor Laura A. **Magee** (CI, WP1 Lead, WP2 Chair) brings to the project her leadership skills as an obstetric physician and Honorary Consultant at King's Health Partners, South London, and an academic, with broad experience with study designs, including mixed-methods research and patient self-reported pregnancy outcomes through the Motherisk Programme, University of Toronto. She has the requisite content and methodological expertise to lead the project, having published extensively on COVID-19 in pregnancy (see Lead Applicant, Research Background) and led national and international collaborations. These have included the Canadian Perinatal Network (16 sites), international CHIPS trial (Control of Hypertension In Pregnancy Study (103 sites, 15 countries), Community-Level Interventions in Pre-eclampsia (CLIP) trials (68 clusters in India, Pakistan, Mozambique, and Nigeria), and most recently, the NIHR-funded WILL trial (When to Induce Labour to Limit risk in pregnancy hypertension) trial in the UK (currently 29 sites).

Ms. Mary **Newburn** (PPIE Lead) has particular expertise in inequalities, as evidenced by her role as Lead, Maternity and Perinatal Mental Health, Applied Research Collaboration (ARC) South London. (For details, see 'PPIE' section of online application.)

Professor Lucilla **Poston** is CI and architect of eLIXIR, a 'living' maternal-child pregnancy cohort in South London. She has renowned skills in building and maintaining interdisciplinary collaborations, and extensive experience, including translating research into policy.

Professor Asma **Khalil** (Out-of-office monitoring co-Lead) is an obstetrician (fetal medicine) and Senior Clinical Lead (Obstetrics), National Maternity and Perinatal Audit, RCOG, UK. She is the inventor of the K2 Hampton app for home BP and blood glucose monitoring.

Dr. Sara **White** (Out-of-office monitoring co-Lead) is a Chemical Pathologist and Metabolic Medicine Physician and Senior Research Fellow (Maternal Diabetes). She has expertise in out-of-office monitoring of GDM by app-guided care before and during the pandemic.

Dr. Ingrid **Wolfe** is a paediatrician and public health physician, with strong academic and clinical ties to community and policy. She is Acting Director, IWCH, KHP; Director, Evelina London Child Health Partnership; Consultant Paediatric Public Health, Evelina London Women and Children's Health.

Debra **Bick** is a thought-leader in UK midwifery with a particular interest in women's physical and mental health and postnatal care. She is Professor of Clinical Trials in Maternal Health, Warwick Clinical Trials Unit, and Editor in Chief of 'Midwifery'.

Professor Peter **von Dadelszen** is an obstetrician (maternal-fetal medicine specialist) with continuous quality improvement expertise, using routinely-collected data to build and externally validate the Pre-eclampsia Integrated Estimate of Risk Scores[78 79]. He has expertise in digital health and will support COVID vaccination work with the CSS Biobank.

Mr. Paul **Seed** is a Senior Statistician with over 30 years of experience in medical statistics, particularly in women's and children's health. He is familiar with diverse study designs, including case-control, cohort, weighted random sampling, randomised controlled trials, longitudinal and cross-sectional designs.

Professor Julia **Fox-Rushby** (Health economics Lead) has >30 years' experience in high-quality policy-driven economic evaluations of the efficiency of investing in improvements to health and wellbeing, and particular expertise in health economics of maternal health NHS studies. She will be assisted by Dr. Marina **Soley-Bori**, post-doctoral Research Fellow, Health Economics, experienced in evaluating patient-level variations in health service use and costs in South London.

Mr. Sergio **Silverio** (WP2 co-Lead) is a Research Associate in Social Science of Women's Health, and the KCL School of Life Course Sciences Qualitative Lead. He has broad expertise in qualitative methods and methodologies for health services evaluation and care research, including thematic framework analysis. Throughout the pandemic, he has held an expansive portfolio of maternity services and perinatal mental health research related to COVID-19. He will oversee the junior qualitative researcher.

Dr. Abigail **Easter** (WP2 co-Lead) is a Senior Lecturer in Maternal and Newborn Health and Deputy Lead, ARC South London Maternity and Perinatal Mental Health Theme. She focusses on improving outcomes for women experiencing perinatal mental illness and, in particular, understanding the interface between physical and mental health and care services during and following pregnancy.

Professor Emma **Duncan** (WP2 co-Lead) will lead the real-time epidemiology. She works closely with the KCL team on the KCL-CSS/ZOE app data, and co-leads the CSS Biobank (with Steves, collaborator). She has particular expertise in databases and epidemiology, and will be supported in this role by Molteni, a biomedical engineer expert in classical statistics and machine learning, who has worked extensively with analysis of KCL-CSS/ZOE data.

Professor Eugene **Nelson** (WP3 Lead), Professor of Community and Family Medicine, The Geisel School of Medicine at Dartmouth, and Director, Population Health and Measurement, The Dartmouth Institute for Health Policy and Clinical Practice, USA. He is the 'father' of

learning health systems, taking learning from data collection through imagining the future and into co-production and implementation. From Nelson's Dartmouth Institute team are: Ms. Aricca **Van Citters**, Senior Program Director, with extensive experience in patient and clinician partnerships to improve health outcomes and support delivery of high-value care for chronic conditions; and Professor Glyn **Elwyn**, Co-Director, Coproduction Laboratory, who will bring his primary care training, collaboration with patients, and understanding of WP2 findings, based on his patient-centred focus and experience advising NHSE.

Dr. Harriet **Boulding** specialises in the qualitative analysis of health systems, maternal and child health policy, and achieving impact from public health research. She has advised the Chief Medical Officer on cross-cutting public health and social policy issues, and has designed training materials for senior civil servants addressing leadership and public health.

Ms. Jane **Brewin**, CEO Tommy's Charity, will support through their website, to recruit KCL-CSS/ZOE app users to the CSS Biobank project (WP2) and disseminate all study results.

KEY COLLABORATORS

(*Letters of support available here for collaborating organisations outside of KCL.)

Dr. James MN **Duffy**, Clinical Fellow, King's Fertility, and planned Academic Clinical Lecturer, KCH 2021-4), is an obstetrician who will offer constructive challenge based on expertise in clinical infertility care and the work of NHS Digital (WP1) and policy (WP3).

Dr. Nathalie **MacDermott**, Academic Clinical Lecturer, KCL, is a paediatrician and infectious diseases expert with lived experience of Long COVID.

Mr. Ken **Hodson**, obstetrician and Head of UKTIS*, has a particular interest in post-marketing surveillance of COVID-19 vaccines in pregnancy (WP1 and WP2).

Professor Rebecca **Reynolds** is PI, 'Born in Scotland', a recently-funded MRC eLIXIR-like data linkage in Scotland using BadgerNet. She will collaborate for generalisability of findings.

Dr. Claire **Steves**, Consultant Physician and Endocrinologist, co-Leads the CSS Biobank with Duncan, and will support as a co-founder of the KCL-CSS/ZOE app.

11. SUCCESS CRITERIA AND BARRIERS TO PROPOSED WORK

Our success criteria will be: successful linkages of eLIXIR with GDm- and BPm-Health apps, the HFEA dataset, and NIMS; publications of physical and mental health outcomes pre-pandemic, pandemic, and post-pandemic; recruitment of representative populations for robust experiential data of maternity service delivery during the pandemic; and generation of a policy pamphlet – a short document that presents the salient features of our findings, in a visually-appealing and easy to read format, designed for policy-makers.

While the major risk to any project success is timelines, the risk in this proposal is minimal.

● eLIXIR is based on opt-out consent, so recruitment is not a challenge. eLIXIR already has in place essential approvals (for linkage of maternity, newborn, maternal mental health, LDN, and HES data) and this project has been approved by the Oversight Committee, so only an amendment is required for linkage with out-of-office monitoring data (for GDm-Health), HFEA (fertility treatment), and NIMS (vaccination). Data from Oct/2018 (eLIXIR inception) to Apr/21 will be available for cleaning and analysis from the start of this project.

● Easter and Silverio, supported by Newburn for recruitment, are experienced in completing qualitative work in South London, with women, partners, care-providers, and policy-makers. Also, our aim to address inequalities related to service reconfiguration will be supported in particular by shared membership with the NIHR ARC, South London. The KCL-CSS/ZOE app already has >4.5 million users throughout the UK, and the CSS Biobank has existing ethics approval to invite app-users to participate in further research; only an amendment is required to specify this particular pregnancy/postpartum/planning pregnancy project.

The applicant is a clinical academic, funded by KCL, and has the full, enthusiastic support of her Head of Department to undertake this work, from Aug/2021.

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