Giant PANDA
Pregnancy ANtihypertensive Drugs: which Agent is best?

Study handbook

V1.1—31/08/2022

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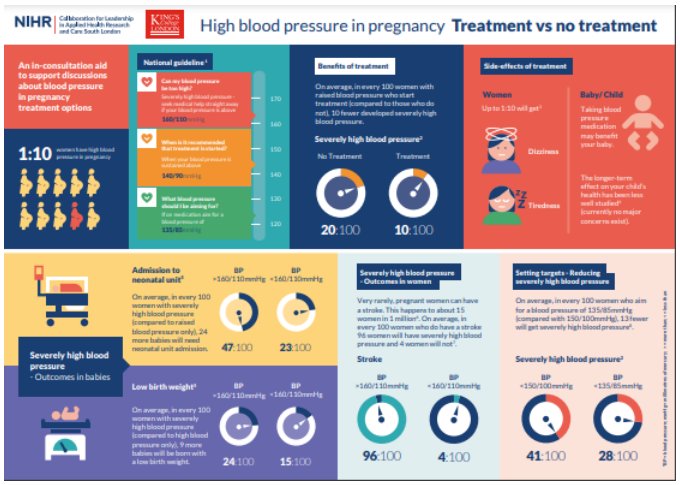
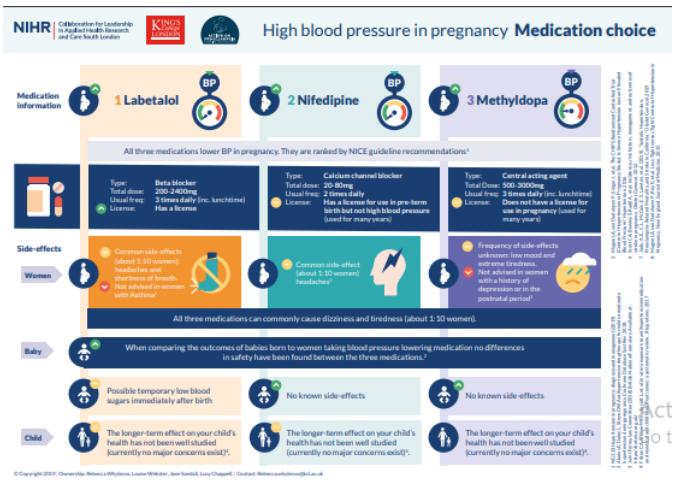
About the study

Background

Approximately 70,000 pregnant women per year (8-10% of UK pregnancies) have hypertension or high blood pressure in pregnancy. This includes chronic (pre-existing, typically essential) and gestational (new after 20 weeks' gestation) hypertension and preeclampsia (hypertension with additional features of multi-organ involvement).

NIHR High BP in pregnancy decision aid: Treatment vs. no treatment and medication choice is accessible here





The NICE Hypertension in Pregnancy: diagnosis and management guideline recommend:

> *"Consider Labetalol to treat chronic hypertension in pregnant women and to consider nifedipine for women in whom labetalol is not suitable, or methyldopa if both labetalol and nifedipine are not suitable. Base the choice on any pre-existing treatment, side-effect profiles, risks (including fetal effects) and the woman's preference". [2019].*

However, data to inform this are sparse. A Cochrane review published in 2018 found that only two trials, totaling 354 women, have compared labetalol vs. nifedipine.

There is wide variation in prescribing of antihypertensives in pregnancy. Although some doctors and women may have preferences, there is inadequate evidence to say whether labetalol or nifedipine is better.

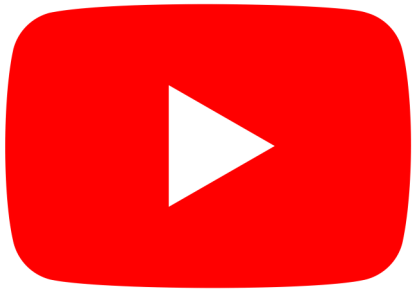
About the study

Aim

The giant PANDA study aims to answer the research question ***'In women with pregnancy hypertension, what is the effect of a treatment strategy with nifedipine versus labetalol on severe maternal hypertension and a composite of fetal or neonatal death, or neonatal unit admissions?'.*** Establishing whether one drug is better for the woman and whether the outcomes for the infant are not worse and adding to the sparse evidence on which women and clinicians share value-based decision-making.

It is a pragmatic, open-label, multi-centred, two-arm RCT of 2,300 pregnant women with hypertension in around 50 consultant-led maternity units across the UK.

We can now make the choice of antihypertensive in pregnancy… *randomised* within the giant PANDA Study, rather than random or arbitrary.



Giant PANDA study summary with Professor Lucy Chappell
(https://youtu.be/5K7_Xaucj2w)

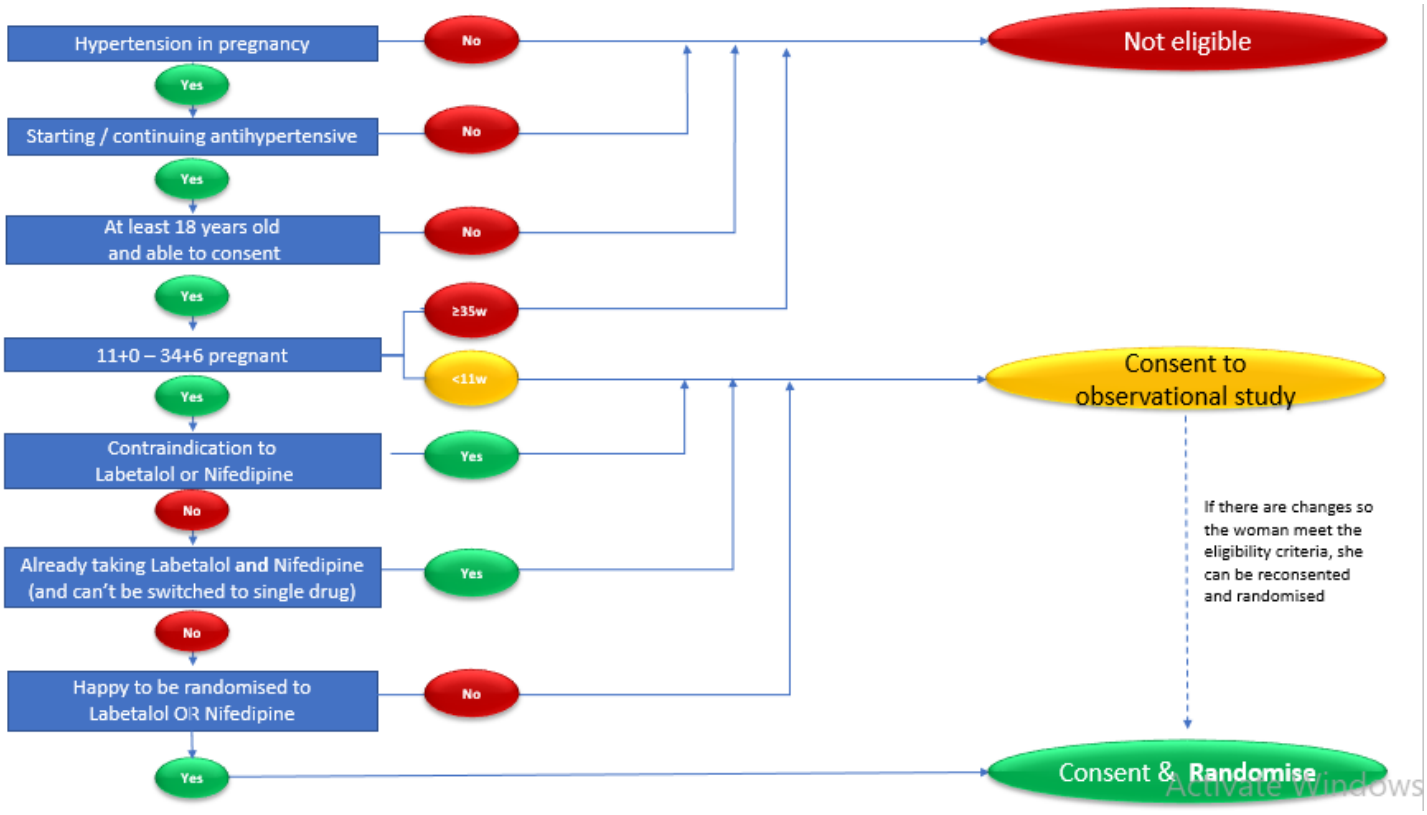
A quick guide to the Giant PANDA study
(https://www.youtube.com/watch?v=4lz80y4sWTY)

Background and Rationale to giant PANDA with Professor Jenny Myers
(https://youtu.be/z66IEwo_Ymc)

About the study

Eligibility

- ✓ Hypertension in pregnancy (chronic or gestational hypertension or pre-eclampsia)
- ✓ Clinician decision made to initiate, or continue use of, an antihypertensive drug
- ✓ 11+0 – 34+6 weeks pregnant (randomised arm only)
- ✓ ≥18 years
- ✓ Able to provide informed consent



Activate Windows

About the study

Approaching and consenting women

i. Are you identifying and screening all eligible women at your Trust?

⇒ Screen bookings – ask your clerks/community midwives to call/email you when they have someone with hypertension

⇒ Screen clinic lists (e.g. maternal medicine, diabetes, renal, hypertension, etc.)

⇒ Check in daily with antenatal clinic, MAU/DAU, antenatal ward and labour ward. Keep reminding them to email / call you.

⇒ Present at your clinical governance / MDT meetings to raise awareness of the trial

⇒ Email the study quick guide to your doctors and midwives (https://www.youtube.com/watch?v=4lz80y4sWTY)

⇒ Keep reminding doctor and midwives to call when they are writing an antihypertensive prescription – key cards, quick reference leaflets on antenatal clinic desks, posters in staff and patient areas, stickers on outpatient prescription drawer and patient information leaflets in home blood pressure service package

⇒ Get an Associate PI! https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm

⇒ And…. repeat! You will need to keep repeating the above steps for the duration of the trial to maintain engagement

Professor Lucy Chappell discusses approaching women to join the Giant PANDA study
(https://youtu.be/O1_D4gBFtP0)

Professor Jenny Myers approaching a woman to join the giant PANDA study
(https://youtu.be/lx7ev5-EfHM)

About the study

ii. Are you maximizing recruitment and follow-up at your Trust?

⇒ Ensure your team (consultants, trainees and midwives) are all 'singing from the same hymn sheet' regarding antihypertensives in pregnancy—this might be achieved by 1-2-1 conversations, a training session with Professor Jenny Myers, distributing our memo 'What you need to know...before prescribing antihypertensives in pregnancy' or 'The quick guide to the Giant PANDA study' (https://www.youtube.com/watch?v=4lz80y4sWTY)

⇒ Approach women with hypertension in pregnancy and start having conversation about options for antihypertensive medication as early as possible in pregnancy. They can consent to the observational study before 11 weeks and then reconsented and randomised at/after 11 weeks, assuming they meet the study eligibility criteria

⇒ We encourage you to offer the giant PANDA study to all women, including those who are currently on antihypertensive medication (and potentially have been for some time) as well as women who require translation for antenatal care. Discussing the study when women are initially starting medication and/or requiring a medication increase can be particularly good opportunities to discuss the giant PANDA study

⇒ Document the option of the giant PANDA study in women's management plans, e.g. "If started on antihypertensives, consider the giant PANDA study—contact the research team".

⇒ Emphasize to women that the study is collecting information about their experiences and satisfaction with the two medications . Alongside the primary aim, this study will provide much more information for women to make decisions about what medication might be right for them

About the study

iii. Learnings from our pilot sites

- Try not to 'gate keep' which women are likely to want to take part
- Offer study participation to all women who are currently on or starting antihypertensive medication in pregnancy
- Ensure women whose BP is controlled and are established on medication, understand, and are willing to be, randomised to either Labetalol or Nifedipine
- Ensure women are willing to start or switch antihypertensive medication
- Please defer any questions you may have about a woman's care plan or medication to the prescriber / care team

Ensure the woman understands:

The giant PANDA study is trying to work out which blood pressure medication in pregnancy works best. We are doing this within a trial by deciding which medication they will get at random by a computer (like tossing a coin) and then that the medication will be prescribed in the usual way by the doctors looking after them.

Both Labetalol and Nifedipine have been used in pregnancy for many years. We know there are benefits and drawbacks of both but we don't have the evidence to conclude which is better.

Switching and adding to antihypertensive medication in pregnancy is common. It can take time to optimise BP control and medication requirements may increase as a pregnancy progresses.

The surveys are key to understanding the differences in these medications.

Please encourage all participating women to complete all the surveys up until the end of pregnancy/ birth

Who she can contact if she has medication or study concerns (e.g. side effects, poor BP control)

If there is inadequate BP control or excessive side effects, their medication can be changed (and they can continue in trial)

Frequently Asked Questions

Can a participating woman's antihypertensive medication be stopped, switched or additional antihypertensives added? And can she still continue to take part in the study?
Yes, you are free to stop/switch/ add to a woman's antihypertensive medication at any point without her discontinuing from the study.

Do we need to involve clinical trials pharmacy?
No, prescribe antihypertensive drugs using your normal methods.

Does the prescribing clinician need to be on the delegation log and/or take consent for the study?
No, this is not necessary. Research midwives and nurses can take consent on the giant PANDA study as the medications being used are routinely used in clinical care. The person taking consent must be on the delegation log and must have a discussion with a doctor/ prescriber confirming that the prospective participant can safely be prescribed labetalol OR nifedipine and can be randomised in the giant PANDA study. This doctor/ prescriber must document that the prospective participant is eligible for the study in the woman's maternity notes. The person taking consent must take the name and GMC number of the doctor/ prescriber and record this in the database.

Do we need to write to a participating woman's' GP?
No, routine methods (or not) of communicating medication changes or requesting repeat prescriptions to GP should be used. The GP is free to stop/switch/ add to a woman's antihypertensive medication at any point without her discontinuing from the study.

Are there changes to a participating woman's antenatal care?
No, routine antenatal care for pregnant women with hypertension (NICE 2019 guidelines) should be followed.

Is there any postnatal follow-up?
No. Outcomes are collected up until primary discharge or 28 days (whichever is soonest).

REDCap database

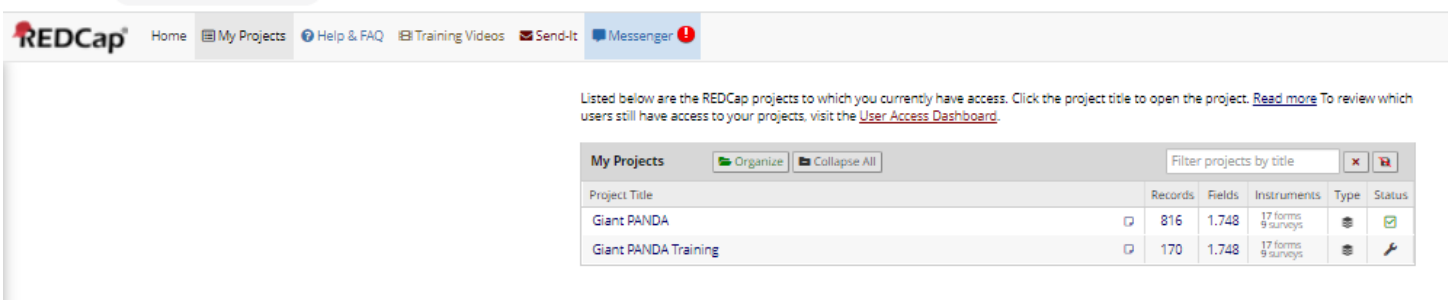
Database training & login

https://bctu-redcap.bham.ac.uk/

The giant PANDA study team will provide training for the study RED-Cap database in advance of your site receiving the 'green light'.

There are two projects on the database (found in 'My Projects'): a training database ('Giant PANDA Training') and a live database ('Giant PANDA').

The training database can be used to familiarize your self with the database.



If you require refresher training or you have a new team member, please contact the giant PANDA study team for training. If you feel confident using the database and you received training directly from the study team, we are happy for you to cascade the training to new team members.

To get your database login please contact the giant PANDA study team with your:

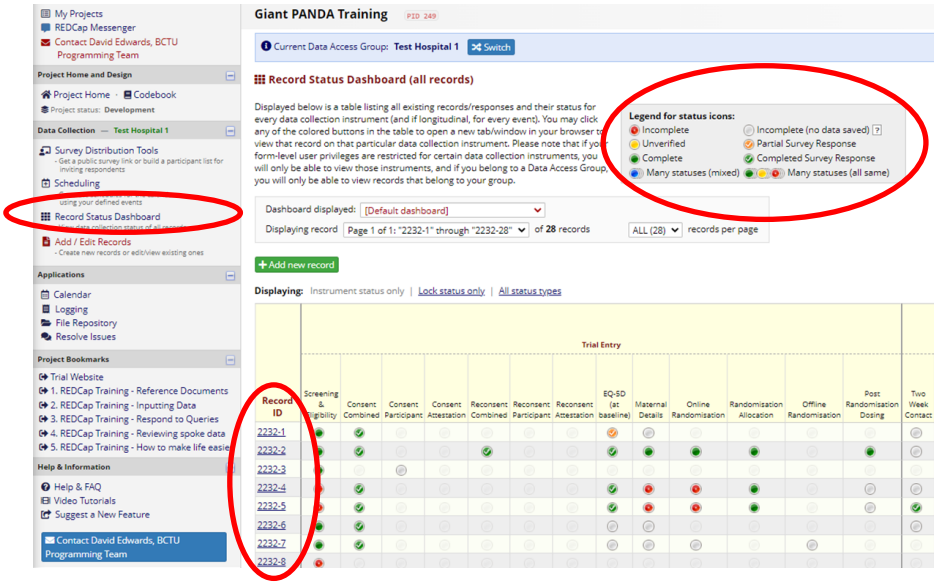
- GCP certificate
- research CV
- signed delegation / training log

The Giant PANDA study database training RECORDED SESSION
(https://youtu.be/vdeLJY7rXY0)

REDCap database

Overview

To view all women approached to take part in the study at your site click 'Record Status Dashboard' on the left hand side of the screen after logging in.



Each 'Record ID' is a woman and each column is a form.

The legend on the right hand side indicates the 'status' of the forms.

Participant & research midwife completed forms:

- Consent *(separate consent forms are available for: face to face consent, remote consent and re-consent)*

Research midwife completed forms:

- Screening & Eligibility
- Maternal Details
- Randomisation

} *Completed **at time of consent***

- Maternal Details (post-randomisation)
- Antenatal Outpatient Preliminary & Contacts
- Antenatal Inpatient Preliminary & Contacts
- Antenatal scans
- Maternal outcomes
- Neonatal outcomes

} *Completed after primary hospital discharge OR 28 days post birth (and before EDD+6weeks)*

Protocol Deviation | SAE (CTIMP) | Change of Status } *Completed as needed.*

Participant completed:

- EQ-5D

} *Completed **at time of consent***

- Two Week Contact
- Four Weekly Contact Survey

} *Completed at set time intervals after consent*

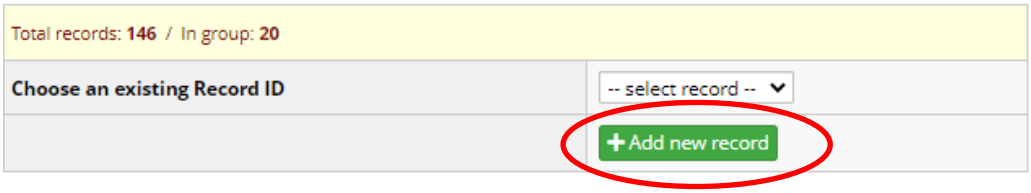
REDCap database

Screening

Please screen all women on the database who you are actively considering for the study e.g. all women you are giving a giant PANDA study participant information leaflet to.

1. Log onto the REDCap database https://bctu-redcap.bham.ac.uk/

2. Click 'Add / Edit records', on left hand side of screen. Then click on 'Add new record'. This will open a new record.



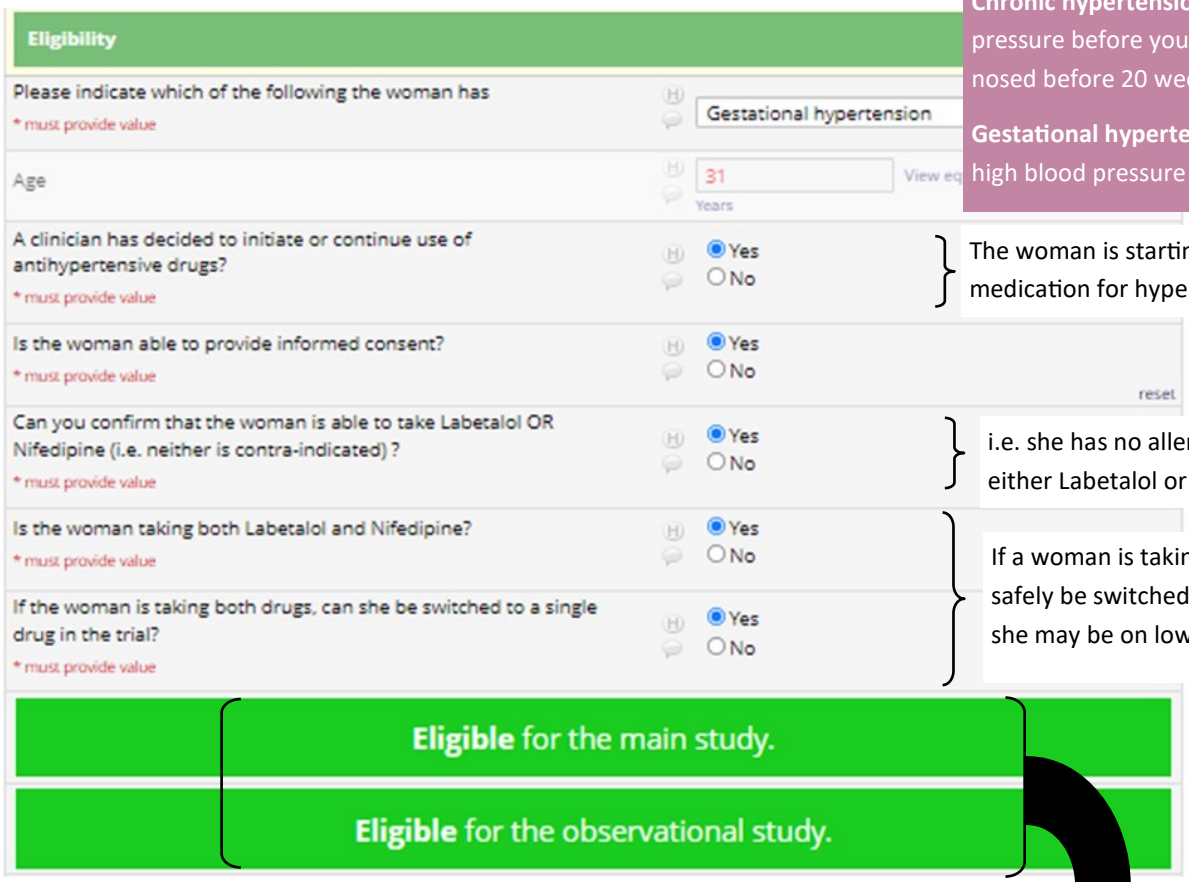
Note: This will create a Record ID for the woman. Please record this in their maternity notes regardless of whether they take part.

3. A new record for this woman will be generated. Open the 'Screening & Eligibility' form by clicking on the 'bubble'

REDCap database

4. Complete the 'Screening & Eligibility' form

Please read *all* the questions *carefully* and answer them accurately for the date/time you are screening them.



Chronic hypertension = having high blood pressure before you get pregnant or diagnosed before 20 weeks

Gestational hypertension = new onset high blood pressure after 20 weeks

The woman is starting **OR** continuing medication for hypertension in pregnancy

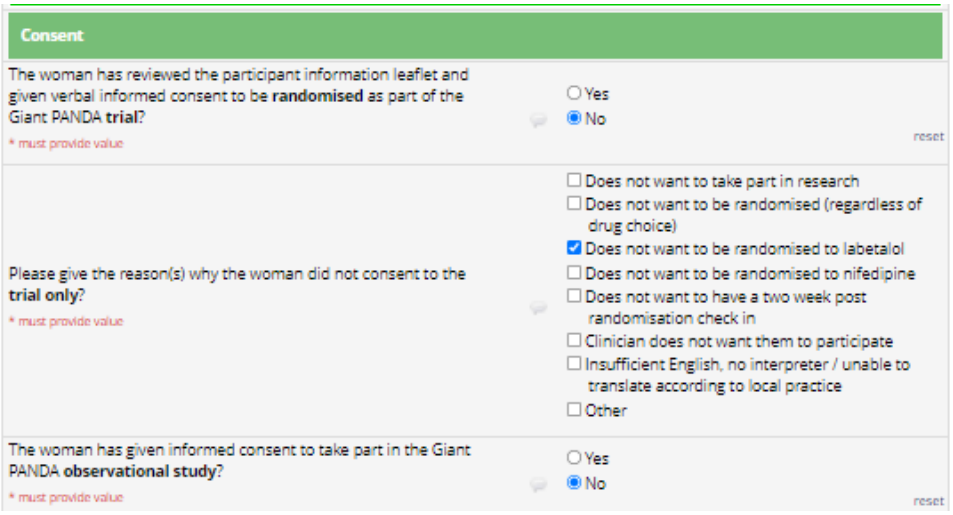
i.e. she has no allergies / interactions to either Labetalol or Nifedipine

If a woman is taking both drugs, can she safely be switched to a single drug? i.e. she may be on low doses of both

Once **all** screening questions have been answered, banners at the bottom of the page will tell you whether the woman is eligible for the giant PANDA study (trial and/or observational study).

REDCap database

We would always encourage you to approach a woman about the randomised study **before** offering the observational study. If she declines, please then offer the observational study.



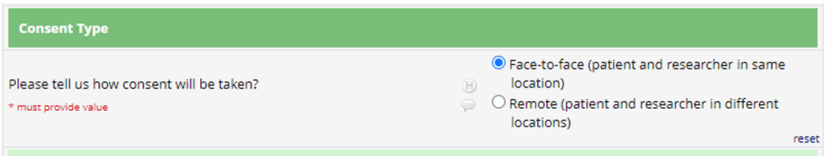
If the woman declines to participate in the study please record the reason why

This form can be updated multiple times if for example the woman changes her mind or their situation changes (e.g. they are now in the correct gestational window). Women can also move from the observational study to the randomised trial.

✓Eligibility for the **randomised trial** needs to be confirmed by the medical professional prescribing the anti-hypertensives (medical professionals confirming eligibility **do not** need to be on the study delegation log) using the normal method (you **do not** need any involvement of the clinical trials pharmacy)

GMC look up (https://www.gmc-uk.org/registration-and-licensing/the-medical-register)

Please document in the women's maternity notes, and on REDCap, that a medical professional is happy for this woman to be part of the trial and whom has confirmed this.

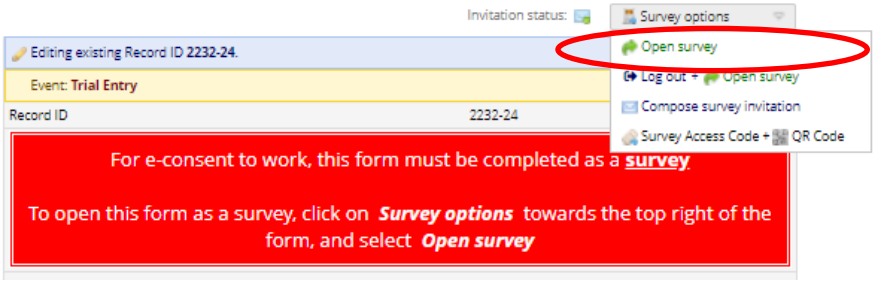


Once all items have been completed please always save the form as '**Complete'** for the following forms to appear

REDCap database

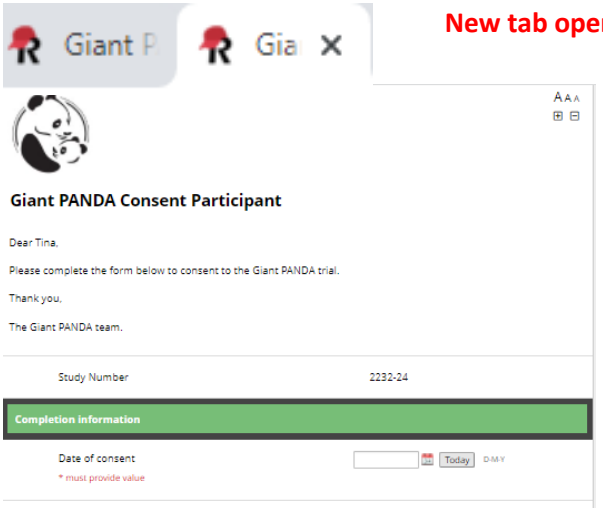
Research Electronic Data Capture

Consent (face-to-face consent)



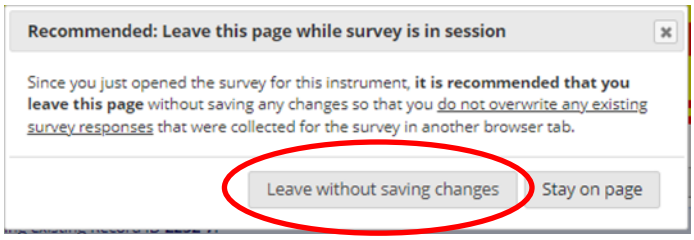
If a woman is happy to participate, open the consent form in **survey mode** within the database and ask the woman to complete the consent form.

New tab opened with consent



The woman should complete the consent form as she would a paper version, reading and answering each of the questions. Apart from the optional questions, the woman must answer all of the questions as 'yes' to be able to participate.

The participating woman will electronically sign the form and the person receiving consent will countersign and complete the final section.



Once the consent form has been completed a pop up message will appear, click 'Leave without saving changes'.

A copy of the completed consent forms should be provided to:

- The participating woman—*this is automatically emailed to the woman on completion*
- Within the woman's maternity notes—*electronically or printed*
- The site file— *printed and saved in your local site file*

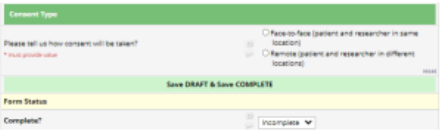
***You can print or save a copy of the consent form at any time**: Open the completed consent form, right-click and select 'print'. Within the 'Destination' dropdown you can either select a printer and 'Print' or 'Save to PDF' and save an electronic version to your computer to upload to the maternity notes*

Note: There is a different consent form for the randomised and observational study. The appropriate consent form will be generated based on the 'Screening & Eligibility' form responses.

REDCap database

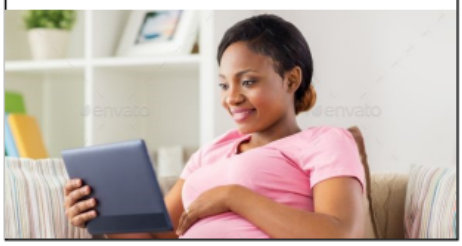
Consent (remote consent)

1. Use the screening and eligibility ' form on REDCap n the same way as normal but opt for 'remote ' (rather than face-to-face) consent at the bottom of the page

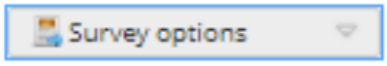


2. This will open up a participant consent form ('consent participant') on the study id.

3. Ensure the woman is prepared to consent and near a computer with her email open.



4. Click on 'participant consent ' form to open. The click on 'survey options' and 'compose survey invitation' and complete the details to send to the woman 'immediately;

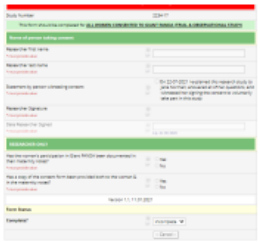


5. Add the woman's email address to the Invitation. You may also wish to change the 'Subject; line to 'Consent for the Giant PANDA Study'. Don't delete anything from the email

6, Let the woman know that you have sent the email and ask he r to complete the consent.

7, Keep refreshing the REDCap page. Once the woman has completed the consent,, you will see a white tick in the green circle next to the 'participant consent' form and the 'consent attestation ' form will be available

8, Complete the 'consent attestation' form by opening and clicking on 'open survey'



9. Print or save a copy of the 'participant consent' and 'consent attestation' forms by opening and right-clicking on form and selecting 'print' then 'save to pdf'' or print to selected printer

Continue the baseline data collection and randomisation (as required) in the usual way

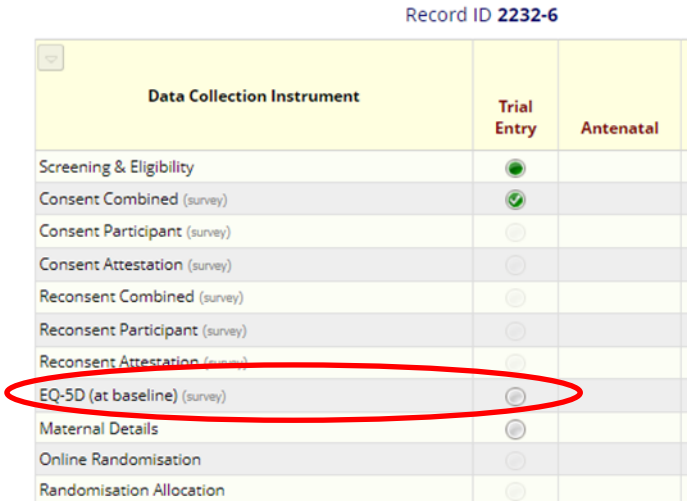
You will need to ensure the woman has a way of collecting/ receiving the prescription

REDCap database

Baseline data collection (*before* randomisation for trial participants)

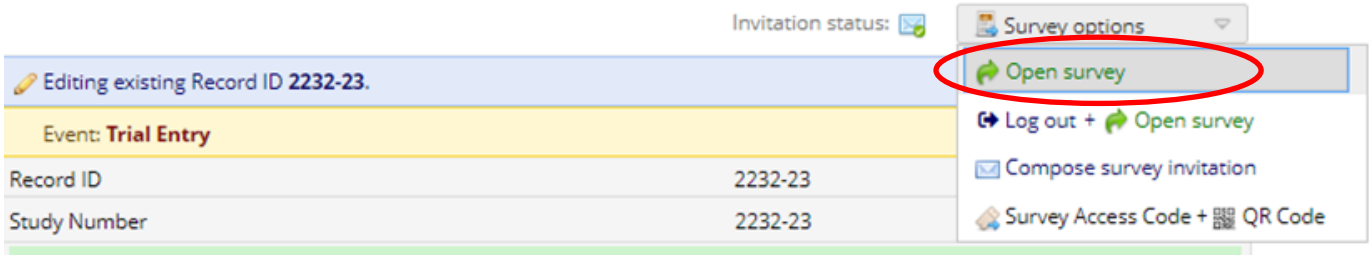
i. EQ-5D form

Following consent, the participating woman will automatically receive a text message inviting them to complete a 5 minute baseline survey.



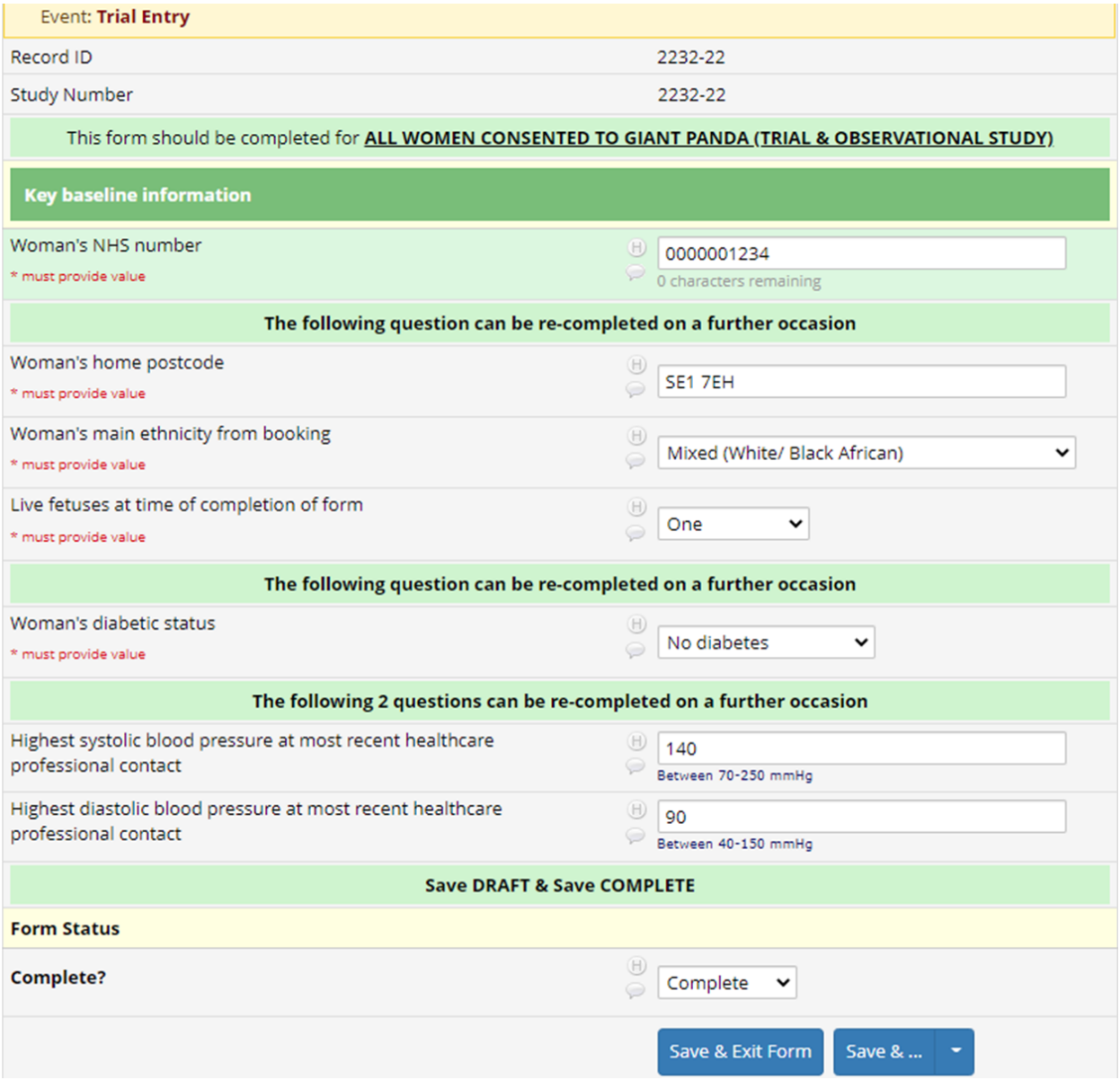
If they are not able to complete the survey using their mobile, or would prefer to complete it using the study tablet, open the 'EQ-5D (at baseline)' form in **survey mode** within the study database and ask the woman to complete the survey.

Ensure the baseline survey is only completed once (i.e. either on the woman's mobile or via the study tablet)



REDCap database

ii. Maternal details form



Event: **Trial Entry**

Record ID	2232-22
Study Number	2232-22

This form should be completed for **ALL WOMEN CONSENTED TO GIANT PANDA (TRIAL & OBSERVATIONAL STUDY)**

Key baseline information

Woman's NHS number * must provide value	0000001234 0 characters remaining

The following question can be re-completed on a further occasion

Woman's home postcode * must provide value	SE1 7EH
Woman's main ethnicity from booking * must provide value	Mixed (White/ Black African)
Live fetuses at time of completion of form * must provide value	One

The following question can be re-completed on a further occasion

Woman's diabetic status * must provide value	No diabetes

The following 2 questions can be re-completed on a further occasion

Highest systolic blood pressure at most recent healthcare professional contact	140 Between 70-250 mmHg
Highest diastolic blood pressure at most recent healthcare professional contact	90 Between 40-150 mmHg

Save DRAFT & Save COMPLETE

Form Status

Complete?	Complete

Save & Exit Form | Save & ...

All data fields within the form are **required** to be completed in order to randomise a woman. This information is used to help to ensure we have a good balance of participants in the two study arms. This form should also be completed for all observational participants.

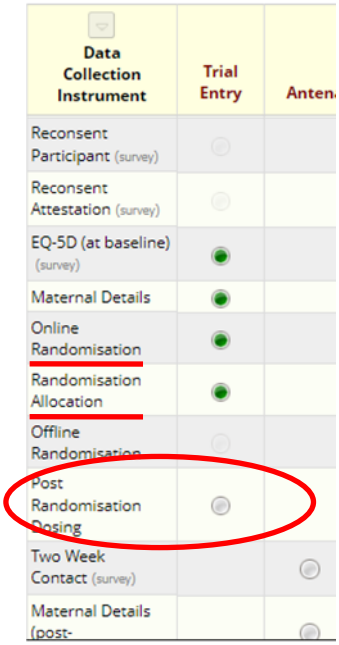
REDCap database

Randomisation (for trial participants only)

Please check that all the information required for randomisation has been **completed** and is **correct at the time of randomisation**. Any missing data, and the corresponding form it is captured in, required for randomization, will be flagged here.

Note: If a woman is being randomised on a different day to consent please check, and document in her maternity notes, that she is still happy to take part.

When you are happy to randomise click ‘Yes’.



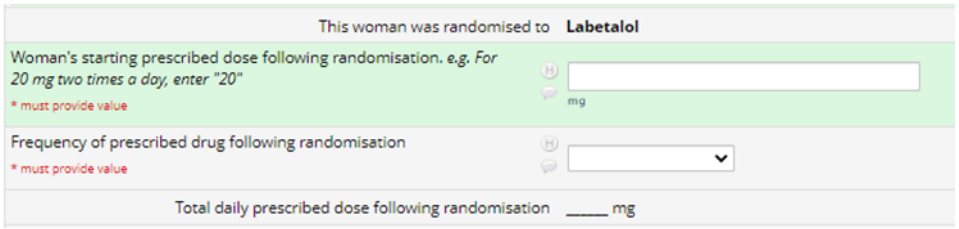
You can see the arm a woman has been randomised to in either the:

- Online randomisation form

or the

- Randomisation allocation form

Once the prescriber has decided on the woman's starting dose, please then enter the prescribed dose within the ‘Post Randomisation Dosing’ form.



REDCap database

Two week contact

Two weeks following consent all participating women will automatically be sent a text message inviting them to complete a 15 minute follow-up survey.

These need to be completed between 2-6 weeks following consent.

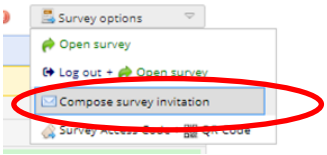
We are really eager to get as close to 100% completeness for these forms. From our pilot sites we have found that the following work well to help achieve this:

Ensuring women who consent to the study are **expecting**, and made aware of the **importance,** of the study surveys

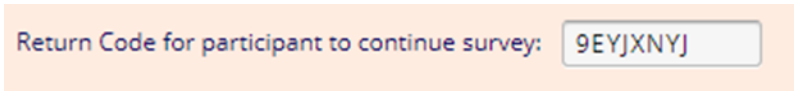
Noting in the team diary when a woman is 2 weeks + 2 days since consent, and checking if the survey has been completed.

Noting in the team diary the woman's antenatal appointment date closest to the 2 week contact and reminding / assist her to complete it.

Reminding women: calling them, texting them or sending reminder emails via the database.



Emails can be sent to participating women via the database by clicking on the 'Compose survey invitation'.



Women who have partially completed a survey will require a 'Return Code' to continue.

Note: two reminder texts are automatically sent to women at 2 day intervals if a survey is not complete.

REDCap database

Monthly contact

At four week intervals all participating women will automatically be sent a text message inviting them to complete a short 5 minute surveys until their:

- Estimated date of delivery (EDD) + 2 weeks

or

- A date of birth/end of pregnancy has been entered within the 'Neonatal Outcomes' form

or

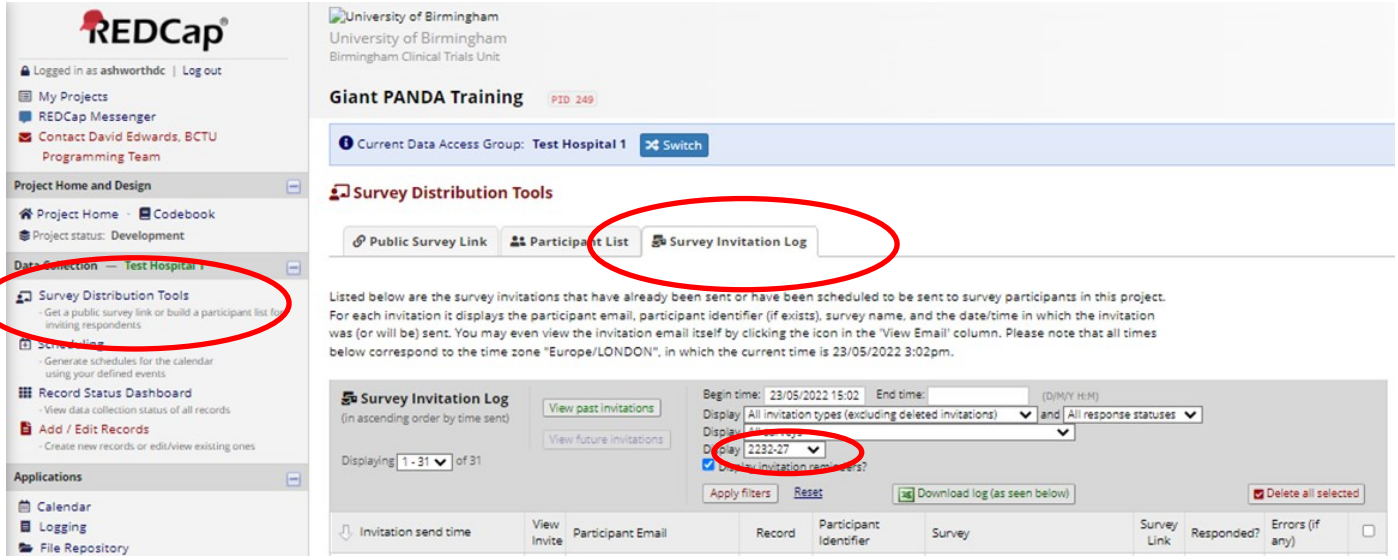
- A 'Change in Status' form has been completed

Reviewing survey invitations & reminders

To view survey invitations and reminders, past and future, click 'Survey Distribution Tools' on the left hand side and then 'Survey Invitation Log'.

To view the a participant's record, select their record ID on the 'Display' dropdown.

In certain circumstances in may not be appropriate to be send survey invitations and/or reminders, if you would like these to be paused/stopped, please get in contact with the giant PANDA team.



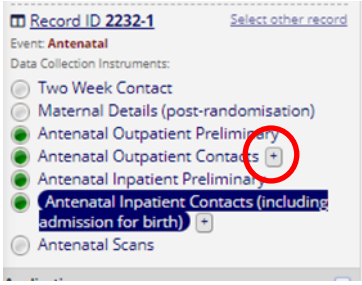
REDCap database

Outcomes

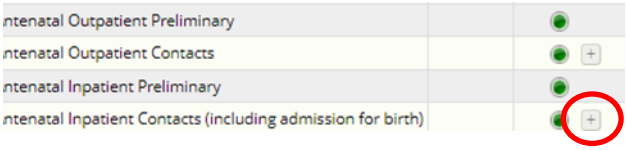
Please complete all outcome forms for a participant by EDD+6 weeks.

- Maternal Details (post-randomisation) } Capturing: obstetric history, booking appointment details, pre-pregnancy medical history and antihypertensive prescriptions before study entry
- Antenatal Outpatient Preliminary & Contacts
- Antenatal Inpatient Preliminary & Contacts

} Captures: blood pressures, antihypertensive prescriptions and side-effects



For each contact (outpatient and inpatient) please complete a new form. To add a form click the '+' button.



- Antenatal scans } Capturing details of the last scan before birth

- Maternal outcomes } Capturing adverse maternal outcomes, split into sections of *before* birth (between consent (observational) or randomisation (trial) up to birth) and *after* birth (after birth up to primary discharge or 28 days post birth, whichever occurs sooner)

- Neonatal outcomes } Capturing birth/end of pregnancy details and characteristics at birth. For multifetal pregnancies one form should be completed for each baby

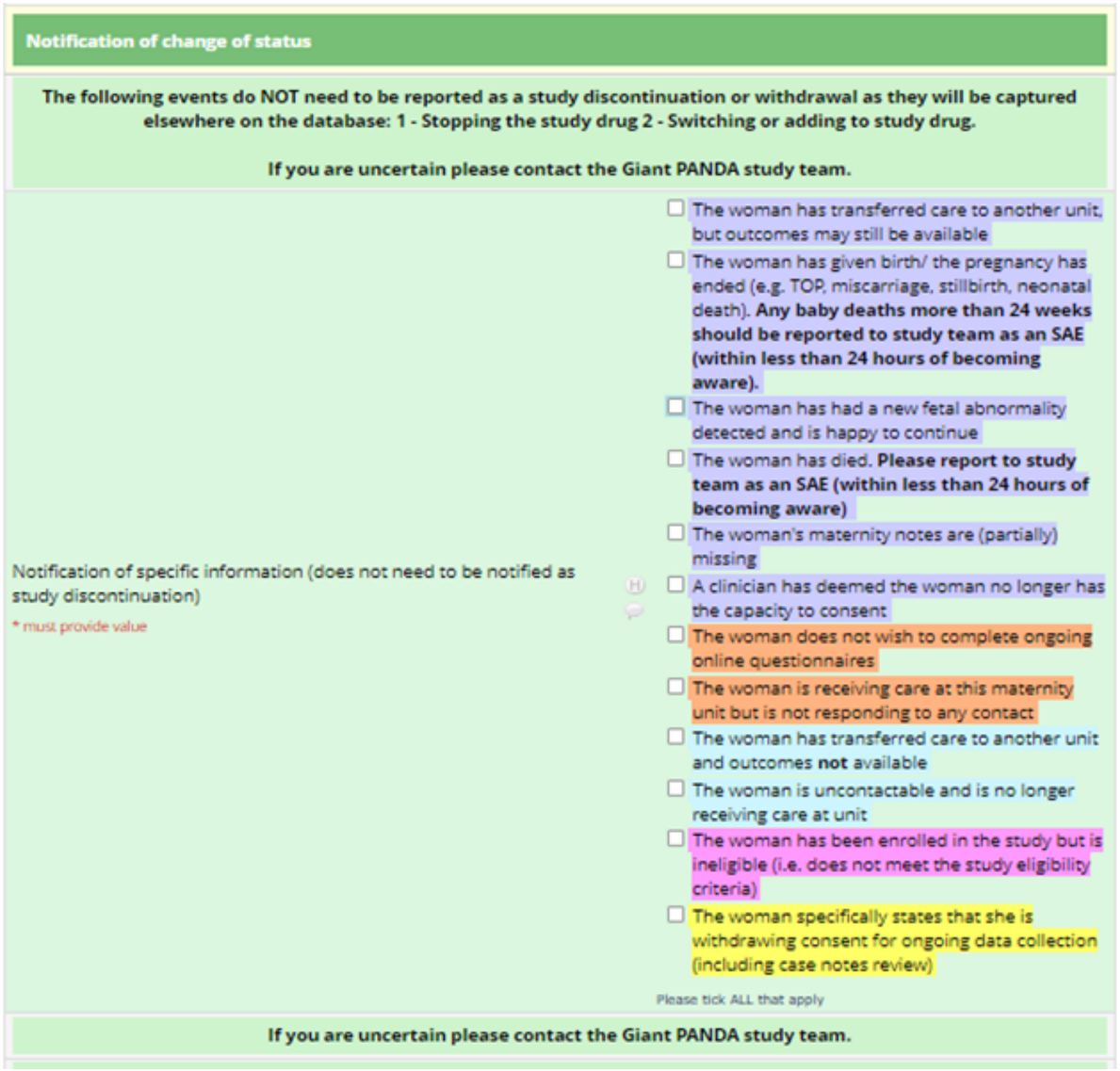
REDCap database

Change in status form

A change in status form should be completed for all women **where there is, or potential for, missing study data** (i.e. baseline AND/OR two-week follow-up AND/OR outcome data).

The form is designed to record and provides **instructions** on what to do. You can update this form as many times as you like. Ensuring this is accurate will reduce the number of data queries your site may receive.

Note: The following events do NOT need to be reported as a study discontinuation or withdrawal as they will be captured elsewhere on the database: 1- Stopping the study drug 2 - Switching or adding to study drug



Notification of change of status

The following events do NOT need to be reported as a study discontinuation or withdrawal as they will be captured elsewhere on the database: 1 - Stopping the study drug 2 - Switching or adding to study drug.

If you are uncertain please contact the Giant PANDA study team.

Notification of specific information (does not need to be notified as study discontinuation)

* must provide value

- ☐ The woman has transferred care to another unit, but outcomes may still be available
- ☐ The woman has given birth/ the pregnancy has ended (e.g. TOP, miscarriage, stillbirth, neonatal death). **Any baby deaths more than 24 weeks should be reported to study team as an SAE (within less than 24 hours of becoming aware).**
- ☐ The woman has had a new fetal abnormality detected and is happy to continue
- ☐ The woman has died. **Please report to study team as an SAE (within less than 24 hours of becoming aware)**
- ☐ The woman's maternity notes are (partially) missing
- ☐ A clinician has deemed the woman no longer has the capacity to consent
- ☐ The woman does not wish to complete ongoing online questionnaires
- ☐ The woman is receiving care at this maternity unit but is not responding to any contact
- ☐ The woman has transferred care to another unit and outcomes **not** available
- ☐ The woman is uncontactable and is no longer receiving care at unit
- ☐ The woman has been enrolled in the study but is ineligible (i.e. does not meet the study eligibility criteria)
- ☐ The woman specifically states that she is withdrawing consent for ongoing data collection (including case notes review)

Please tick ALL that apply

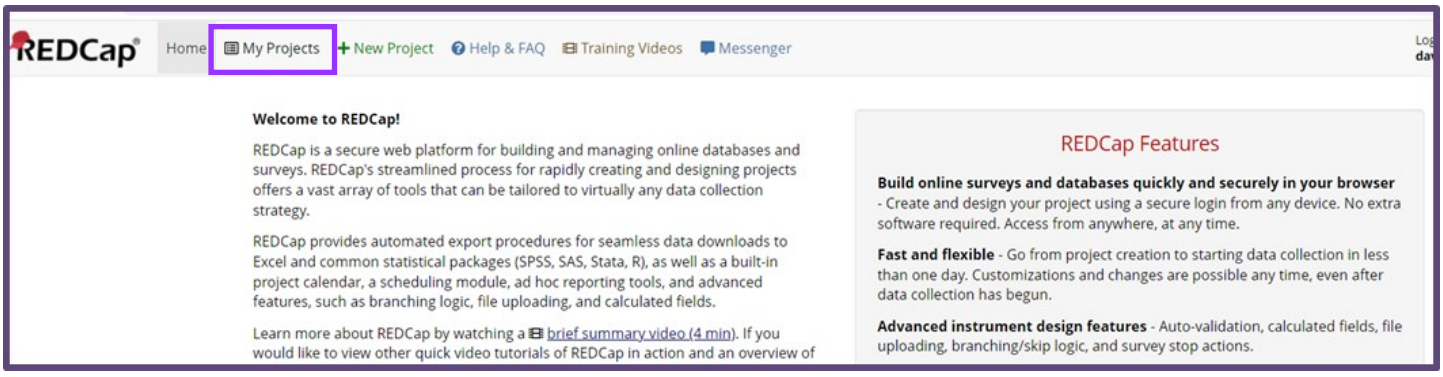
If you are uncertain please contact the Giant PANDA study team.

REDCap database

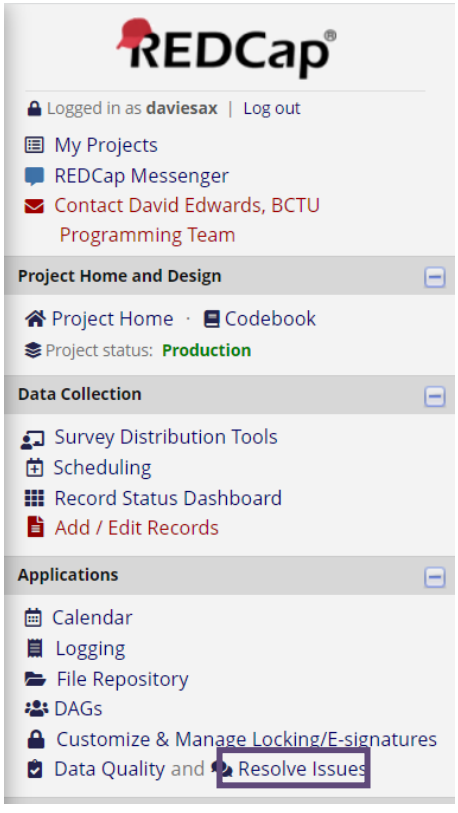
Data queries management user guide

i. Locating data queries within the database

- Navigate to the Giant PANDA page through **'My Projects'** (see below):



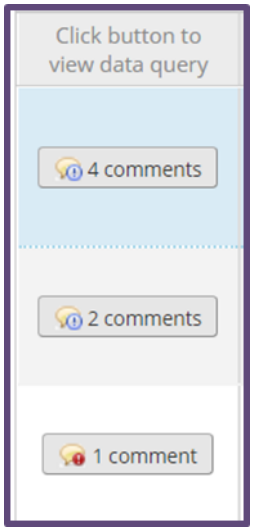
- Click on the project 'Giant PANDA`.
- On the left hand navigation bar, select **'Resolve Issues'** (see below):



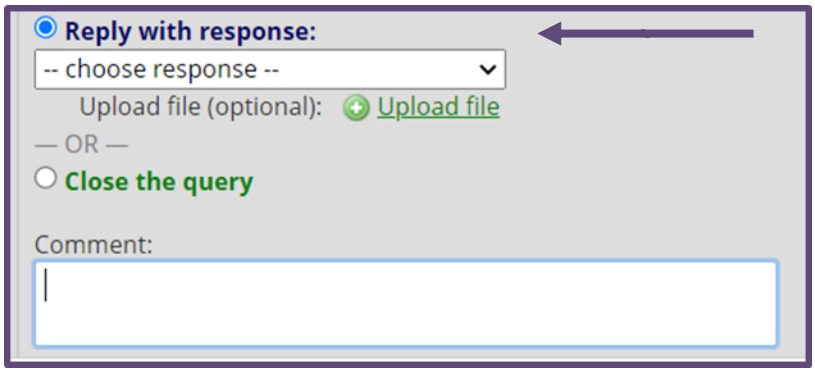
- This page will provide a list of all existing Data Queries for your site, within the Giant PANDA Trial.

ii. Responding to data queries

- To view a Data Query in its entirety, please click on the comments box to the left of each query individually.



- Please provide a response to each query within the comments box.
  - For example, if a query states "This form has not been completed. Please can the missing data be provided or a reason provided for why this information is not available? Thank you." , we would expect one of the following responses:
    ⇒ entering of missing data and confirmation that the form has now been completed within the query
    ⇒ an explanation within the query as to why the information is unobtainable
  - Please note: if a participant's status within the trial has changed and there is missing data/the possibility of missing data (e.g. withdrawn, miscarried, transferred care to another unit, maternity



- If you have answered a query and it has not been closed by the trials team, this has been sent back to you for further attention with instructions. Please read these carefully.
- Please ensure that your wider team are aware of how to prevent and/or resolve common data queries at your site

If you have any questions about a specific query, please email Giant PANDA's Data Manager – Abbie Evans (a.evans.10@bham.ac.uk)

REDCap database

Please contact us the giant PANDA study team if you suspect:

- ***a trial participant has had an SAE***

AND/OR

- ***you/a team member has deviated from the protocol***

Serious Adverse Events

AEs are commonly encountered in this population of pregnant women. As the safety profiles of labetalol and nifedipine are well characterized, a strategy of targeted reporting of AEs will therefore not affect the safety of participants.

We require expedited reporting for the following SAEs:

- Maternal death
- Maternal stroke
- Stillbirth after 24 weeks' gestation
- Neonatal death up to 28 days

These SAEs should be reported both to the giant PANDA team and via the study database (SAE form) within **24 hours of becoming aware**, even if you do not have all the information. The form can be updated when the additional information is received.

Once the SAE form has been completed, please print the form, ask the PI to review and sign in 'wet ink'. Then scan and email the completed form to the giant PANDA study team and keep one copy in your site file.

Note: Other adverse events are expected in this population and will be recorded within the outcome data

Protocol deviation form

If there has been a deviation from the protocol for any reason, please let the giant PANDA team know and complete the protocol deviation form on the database.

Protocol deviations may relate to: inclusion/exclusion of participants, informed consent, randomisation, confidentiality and data protection and/or other reasons.

Contact us

Study website

https://www.birmingham.ac.uk/research/bctu/trials/womens/giantpanda/index.aspx

Study email

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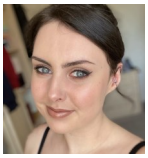
Lead Research Midwife

Hannah Wilson, Hannah.1.Wilson@kcl.ac.uk 07921317891

Clinical Trial Fellow

Danielle Ashworth, Danielle.c.ashworth@kcl.ac.uk 07894336088



Data Manager

Abbie Evans, a.evans.10@bham.ac.uk 01214143902