KING'S College LONDON

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

Giant PANDA

Pregnancy ANtihypertensive Drugs: which Agent is best?

Agenda

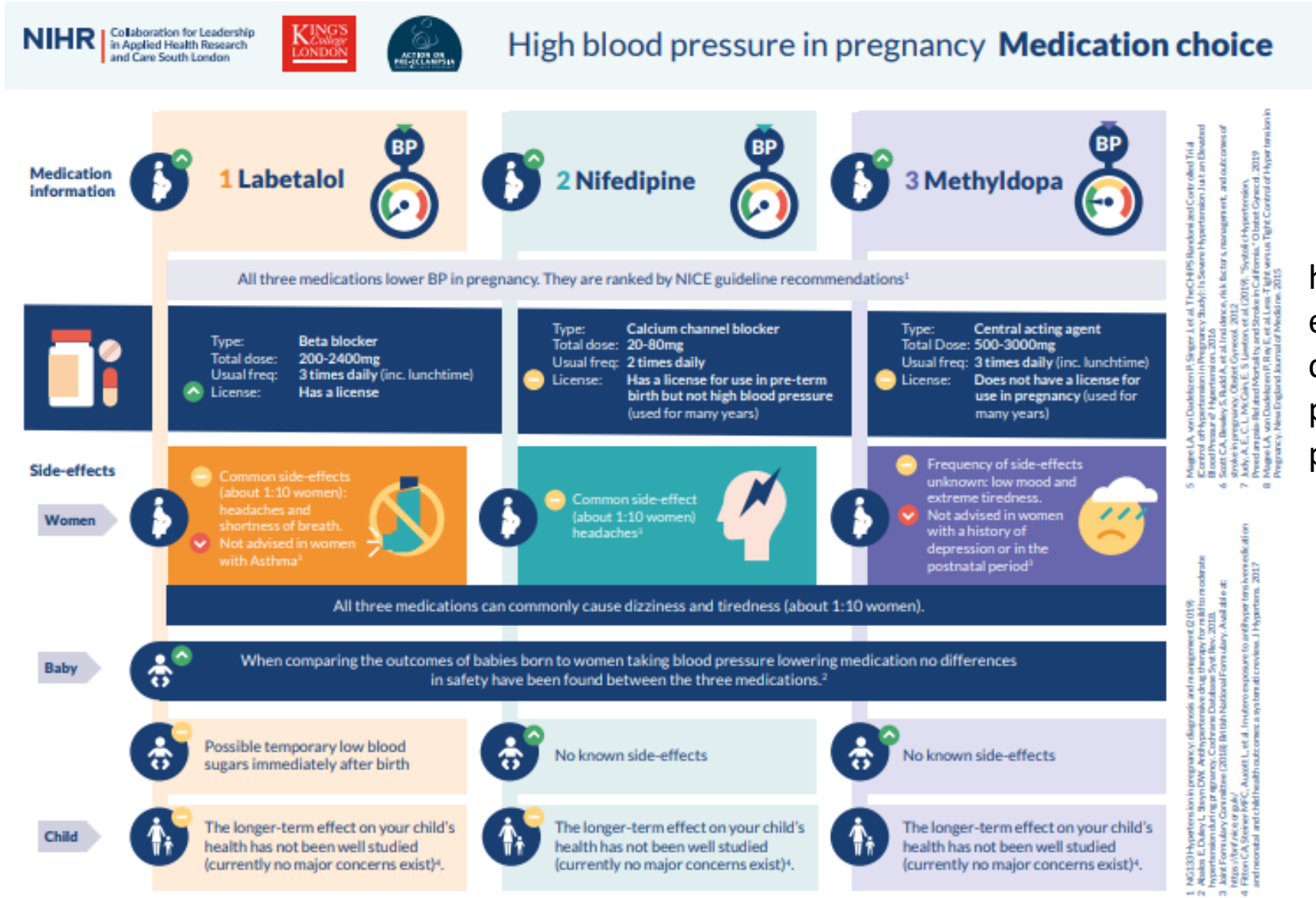
1. Introductions - 5 mins
2. Background and rationale - 10 mins
3. Recruitment, follow-up and outcomes - 15 mins
4. Trial conduct - 5 mins
5. Q&A - 15 mins
6. *Database session – Date TBC (shortly before recruitment starts)*

Background and rationale

Hypertension in pregnancy and medication

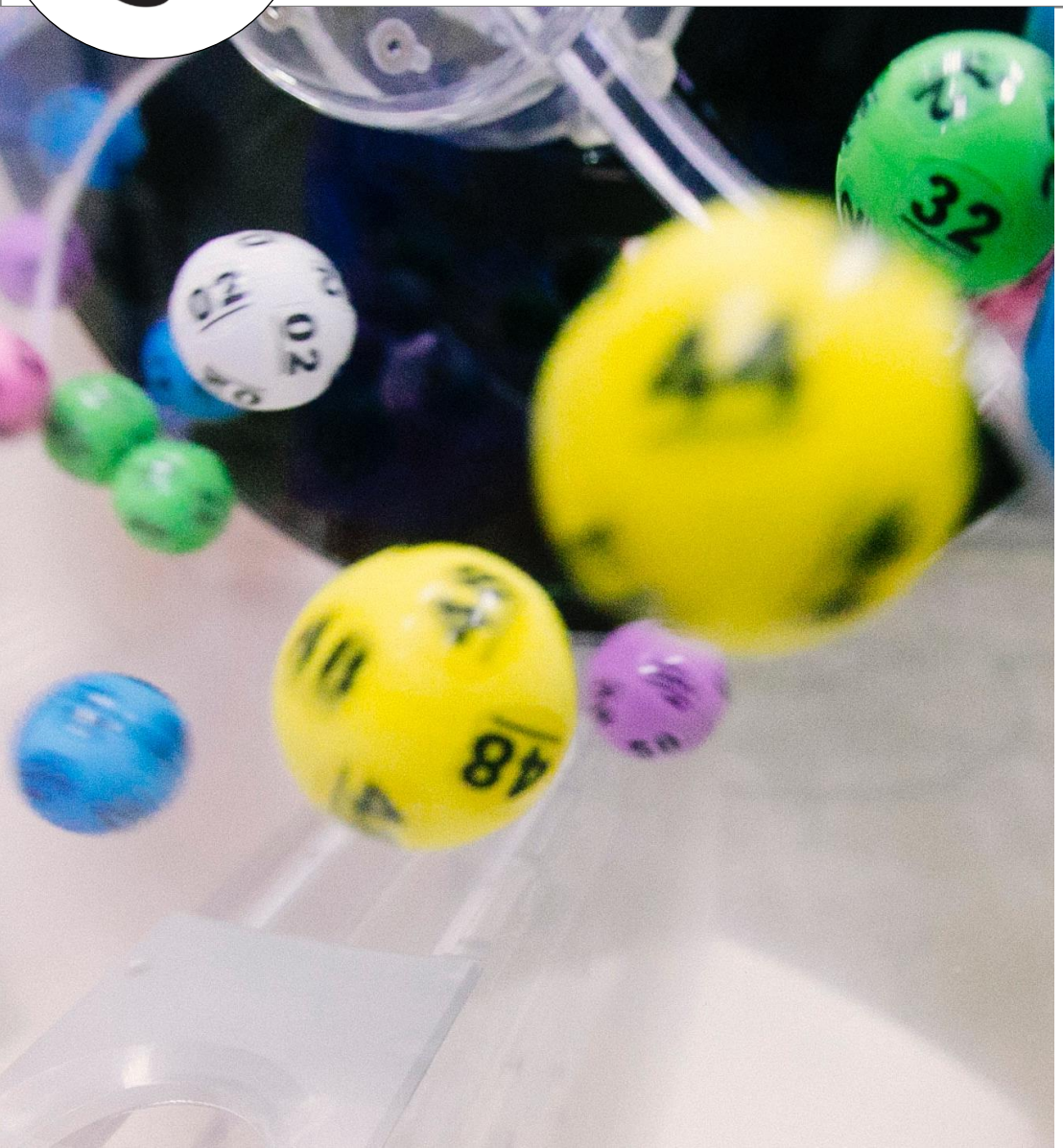
- 1 in 10 pregnant women have high blood pressure during pregnancy
- On average, in every 100 women with hypertension who are on antihypertensive treatment (compared to those who do not), 10 fewer developed severely high blood pressure
- Very rarely, pregnant women can have a stroke. This happens to about 15 women in 1 million
- On average, in every 100 women who do have a stroke, 96 women will have severely high blood pressure

High blood pressure in pregnancy – choice of medication



https://action-on-pre-eclampsia.org.uk/public-area/high-blood-pressure-in-pregnancy/#resources

Wide variation in UK prescribing

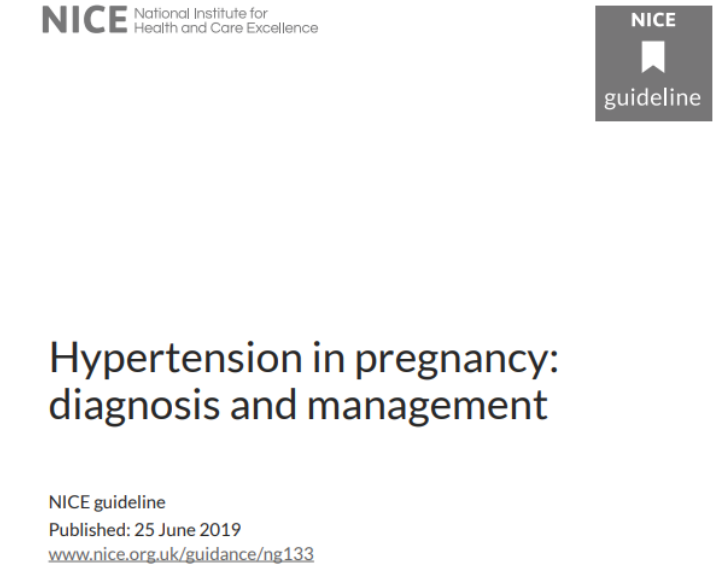


- Wide variation in prescribing of antihypertensives in pregnancy in the UK
- Variation in prescribing observed by:
  - Region
  - Maternity unit
  - Doctors
  - Women
- Some obstetricians report ‘preferences’ for particular antihypertensive medications

Evidence for choice of antihypertensive in pregnancy is sparse

- 2018 Cochrane review of antihypertensives for hypertension in pregnancy included findings from 58 trials, 5909 women
  - **Only two trials, a total of 354 women, compared labetalol and nifedipine**
- The meta-analysis indicated that beta-blockers and calcium channel blockers appear more effective than methyldopa in avoiding severe hypertension (11 trials, 638 women; RR 0.70; 95% CI 0.56-0.88)
- Cochrane concluded:

  "Antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension… If antihypertensive drugs are used, beta blockers and calcium channel blockers appear to be more effective than the alternatives for preventing severe hypertension. ***High-quality, large-sized randomised controlled trials are required in order to provide reliable estimates of the true benefits and adverse effects of antihypertensive treatment for mild to moderate hypertension.*** *We need to know the effects for both mother and baby, as well as the costs to the health services, to women and to their families."*
- NICE (2019) hypertension in pregnancy guideline reinstated this research need



PANDA feasibility study (2017)

- 4 centre feasibility RCT (modified release nifedipine vs labetalol)
- Recruited:
  - 114 pregnant women with chronic hypertension
  - 2.6 women/centre/month (1.2 to 3.7)
- 66% of women approached agreed to participate (included women willing to switch from their current antihypertensive)
- Although the sample size was not large enough to detect clinical effectiveness, it found:
  - 7.4mmHg (−0.4 to −14.4) difference in central aortic pressure
  - 1.2mmHg (-4.9 to 7.2) mean difference in maximum systolic brachial BPs
  - 0.3 mmHg (-2.8 to 3.4) mean difference in mean systolic brachial BPs
  - Adverse events: 38% vs 26%
- PANDA has informed the: acceptability, feasibility, recruitment rate & primary outcome event rate for Giant PANDA

Webster, L. M., J. E. Myers, C. Nelson-Piercy, K. Harding, J. K. Cruickshank, I. Watt-Coote, A. Khalil, C. Wiesender, P. T. Seed, and L. C. Chappell. 2017. 'Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy: A Randomized Controlled Trial', Hypertension.

Giant PANDA summary

Research question	In women with pregnancy hypertension (*Population*), what is the effect of a treatment strategy with nifedipine (*Intervention*) versus labetalol (*Control*) on severe maternal hypertension (*Outcome*) and a composite of fetal or neonatal death, or neonatal unit admissions (*Outcome*)?
Primary objective	To evaluate if treatment with nifedipine (calcium channel blocker), compared to labetalol (mixed alpha/beta blocker) in women with pregnancy hypertension, reduces severe maternal hypertension without increasing fetal or neonatal death, or neonatal unit admission.
Secondary objective	To investigate the effect of treatment with nifedipine versus labetalol on other secondary maternal and fetal/neonatal outcomes including patient-reported outcome measures. To evaluate the cost-effectiveness of nifedipine versus labetalol as antihypertensive drugs from an NHS perspective.

Giant PANDA summary

Trial Design	A pragmatic, open-label, multicentre, two-arm RCT
Setting	50 consultant-led maternity units across the UK
Sample Size	2,300 pregnant women with hypertension
Eligibility	**Inclusion criteria:** ✓ pregnant women between 11^{+0} and 34^{+6} weeks' gestation inclusive ✓ pregnancy hypertension (chronic or gestational hypertension or pre-eclampsia) ✓ clinician decision made to initiate or continue use of an antihypertensive drug ✓ aged ≥18 years ✓ able to provide informed consent **Exclusion criterion:** × contraindication to either labetalol or nifedipine × already taking both labetalol and nifedipine and not able to be randomised onto a single drug

Giant PANDA summary

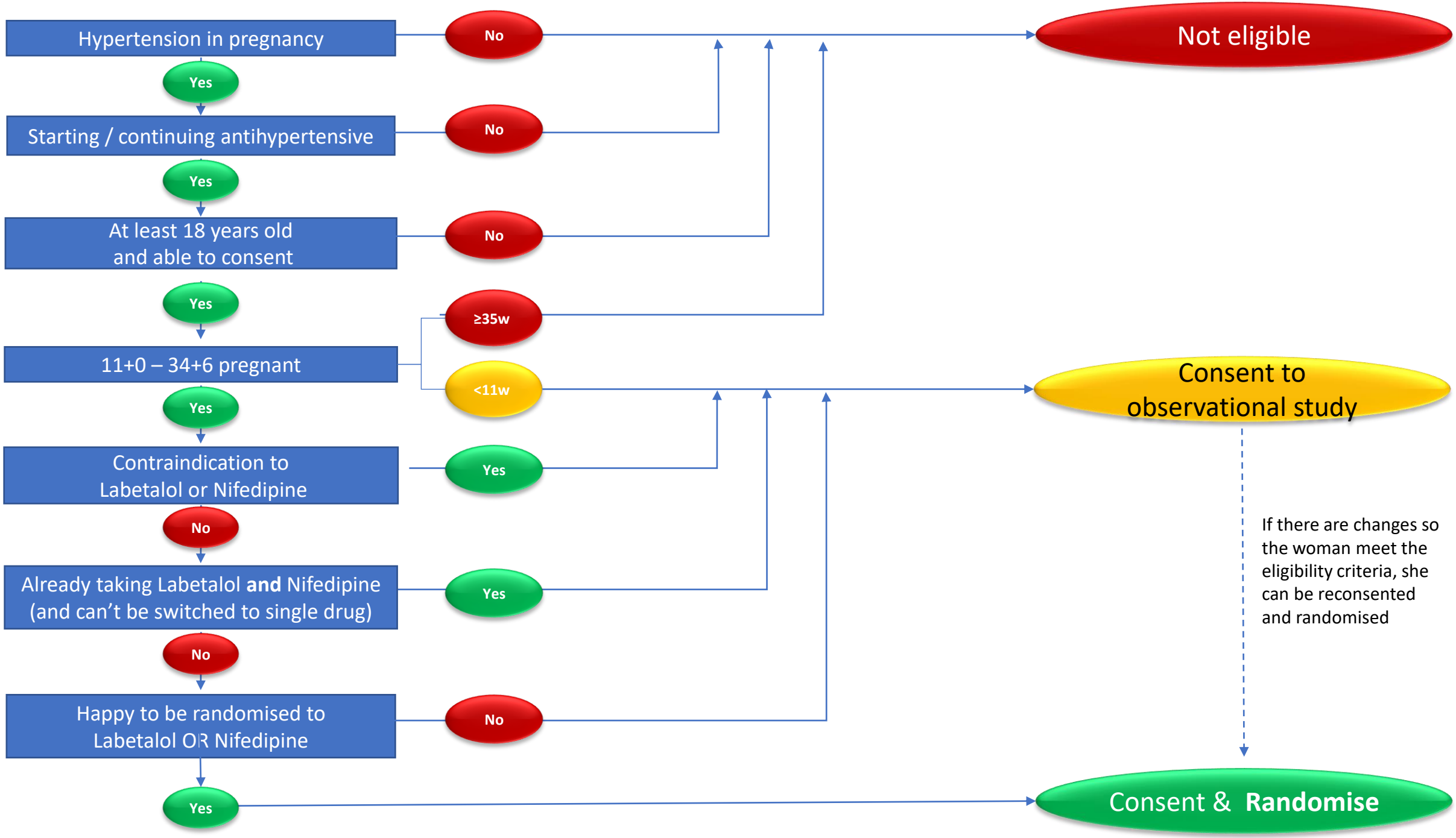
Interventions	Any preparation of **modified release nifedipine**, a calcium channel blocker, (intervention arm) versus Any preparation of **labetalol**, a mixed alpha/beta blocker, (active control arm) by random allocation (1:1) *All other aspects of antenatal and delivery care will follow usual clinical care pathways underpinned by NICE 2019 guidelines for pregnancy hypertension.*
Outcomes	**Primary maternal outcome:** Severe hypertension (proportion of days with a healthcare professional measured systolic blood pressure reading ≥160 mmHg between randomisation and birth). **Primary fetal/neonatal outcome:** Composite of fetal loss before birth or known neonatal death, or neonatal unit admission between randomisation up to primary hospital discharge or 28 days post-birth, whichever occurs sooner (with no double counting of outcomes). **Secondary maternal and fetal/neonatal outcomes:** includes clinical and patient-reported outcomes in addition to health care resource use.

Recruitment, follow-up and outcomes

Identifying eligible women

- Hypertension in pregnancy (chronic or gestational hypertension or pre-eclampsia)
- Clinician decision made to initiate or continue use of an antihypertensive drug
- Booking – 34+6

- ✓ Antenatal clinic
- ✓ Specialist clinics (i.e. mat med/ diabetes/ hypertension)
- ✓ MAU/ DAU/ Triage
- ✓ Antenatal ward
- ✓ Labour ward


Hypertension in pregnancy
No
Not eligible
Yes
Starting / continuing antihypertensive
No
Yes
At least 18 years old
and able to consent
No
Yes
≥35w
11+0 – 34+6 pregnant
<11w
Consent to
observational study
Yes
Contraindication to
Labetalol or Nifedipine
Yes
No
Already taking Labetalol and Nifedipine
(and can't be switched to single drug)
Yes
If there are changes so the woman meet the eligibility criteria, she can be reconsented and randomised
No
Happy to be randomised to
Labetalol OR Nifedipine
No
Yes
Consent & Randomise

Recruitment in the pregnancy journey

1st trimester | 2nd trimester | 3rd trimester

11 weeks

35 weeks

Antenatal clinic

Specialist clinics

Antenatal ward

MAU/DAU/Triage

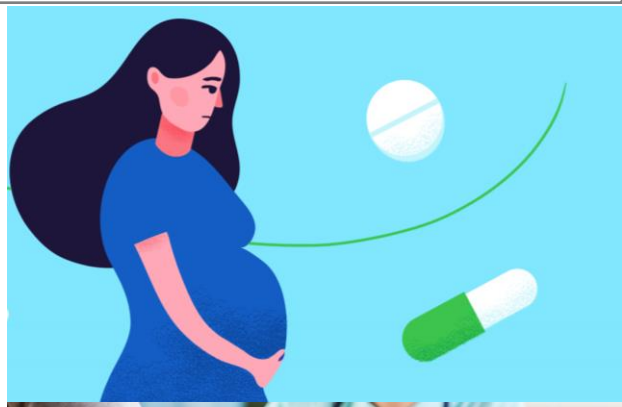
Labour ward

Examples of 'good times' to recruit. For women with:

- ✓ Chronic hypertension – when they **start** medication OR when their medication needs to be **switched/increased** (*Note*: women already on medication can be recruited & randomised)
- ✓ Gestational hypertension – women who are **diagnosed** with GH in MAU/ Antenatal ward/ Labour ward OR when their medication needs to be **switched/increased**. *Note*: women can recruited & randomised immediately (as long as it is safe) or randomised after they have received a stat dose
- ✓ High risk of high blood pressure – add a leaflet to their home BP monitoring pack so women aware of the study before starting medication.

Approaching and consenting women to giant PANDA

- Try not to ‘gate keep’ who is likely to want to take part in the study
- Be clear about the options for someone who is established and controlled on medication. There should be an explicit discussion about being randomised to the alternative medication and what that might mean
- There needs to be a willingness to start or switch antihypertensive medication
- Ensure the woman understands that:
  - Both Labetalol or Nifedipine have been used in pregnancy for many years. We know there are benefits and drawbacks of both medications. We do not have the evidence to conclude which one is better
  - Switching and adding to antihypertensive medication in pregnancy is common. It can take some time to optimise BP control. Requirement for medication may increase as the pregnancy progresses
  - If there is inadequate control or side effects, medication can be changed (and woman can continue in trial)
  - Who she can contact if she has concerns (e.g. side effects, poor control)
  - The follow-up surveys (i.e. the woman’s perspective) are key to understanding these medications
- Defer medication questions you are unsure about to her prescriber/ care team



Consent, randomisation and follow-up and outcomes (REDCap)

Identifying women who may be suitable/eligible & approach them to ask if they wish to participate in the trial

Informed e-consent

Baseline eCRF completion + maternal survey (5-10 minutes)

Randomise (randomised participants only)

Prescribe medication using usual local method (paper or electronic)

Usual antenatal care pathway underpinned by NICE 2019 guidelines
(including guidance and support on treatment regimen, for titration of antihypertensive drugs)

Safety check + two week follow-up survey (max. 30 minutes)

Monthly follow-up survey (max. 5-10 minutes)

End of pregnancy / birth

Maternal and neonatal outcomes
(up to primary discharge or 28 days post birth)

- ✓ You are free to stop/ switch/ add to a woman's antihypertensive medication at any point without her discontinuing from the study
- ✓ No clinical trials pharmacy – prescribe using normal methods
- ✓ No GP letter. Routine methods (or not) of communicating medication changes to GP should be used
- ✓ Follow routine antenatal care for pregnant women with hypertension (NICE 2019 guidelines)
- ✓ No postnatal follow-up

Outcome data

- Outcomes will be collected from consent - primary hospital discharge or 28 days post-birth (if she/the baby remains in hospital)
- Please complete outcomes contemporaneously
- All maternal and neonatal outcomes should be completed by 6 weeks postnatal
- A '**change in study status'** form should be completed for all women where there is missing information or you may no be able to complete all of the outcomes (i.e. missing baseline eCRF + two-week follow-up + outcomes)

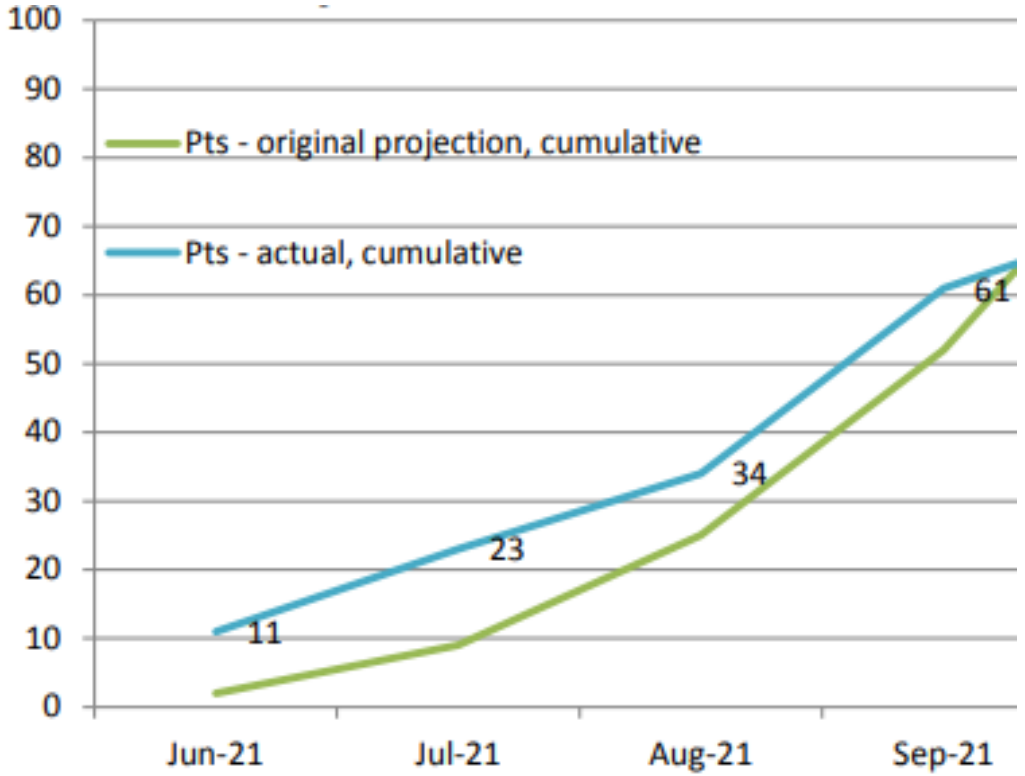
Recruitment

Study targets:

- Recruitment duration – up to 24 months (including internal pilot)
- Total study recruitment target – 2,300 women, ~ 50 maternity units

Site targets:

- Proposed monthly recruitment target – 4 participants per month per site (including women with chronic hypertension, gestational hypertension and pre-eclampsia)
- We need all sites to meet (or exceed) their minimum target each month to meet our target on time



	Jun-21	Jul-21	Aug-21	Sep-21
Pts - original projection, cumulative	2	9	25	52
Pts - actual, cumulative	11	23	34	61

Trial conduct

Something has changed with a participant since randomisation?

A change in study status should be completed for all women where there is or potential for missing study data (i.e. follow-up, outcomes)

The 'change in study status' form is designed to record and provides instruction on what to do if a woman:

- has transferred care to another unit
- has had a pregnancy loss
- had a new fetal abnormality detected and is happy to continue
- has died
- maternity notes are missing
- no longer has the capacity to consent
- does not wish to complete ongoing online questionnaires
- is not responding to any contact
- has transferred care to another unit and outcomes not available
- is uncontactable and is no longer receiving care at unit
- has been enrolled in the study but is ineligible
- said she is withdrawing consent for contact for ongoing questionnaires / case note review

Please **contact us** if you need any guidance when completing this form

See slide 33 for contact details

Serious Adverse Events

Please report the following as SAEs on REDCap

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

Please **contact us** if you need any guidance when completing this form
See slide 33 for contact details

These should be reported on REDCap within **24 hours of becoming aware**, even if you do not have all the information. The SAE report form can be updated when the additional information is received.

When an SAE occurs, it is the responsibility of the PI to review all documentation (e.g. hospital notes) related to the event and ensure it is documented on the SAE form

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

Deviated from current protocol?

The most up-to-date protocol should be stored in your site file and followed at all times

One individual should take responsibility for ensuring all members of the team are trained appropriately and aware of any changes to the protocol

If there has been a deviation from the protocol for any reason, please complete the **protocol deviation form** on REDCap

This includes deviations related to:

- Inclusion/exclusion of participants
- Informed consent
- Randomisation
- Confidentiality and data protection
- Other protocol deviations

Please **contact us** if you need any guidance when completing this form

See slide 33 for contact details

“Paperwork”

- All trial CRFs including consent should be completed on REDCap (unless impossible!)

- For a Giant PANDA database login, please schedule a ‘database training’ session and email the study team copy of your:
  - CV
  - GCP
  - Signed delegation log
  - Signed training log

- **Note:** *Medical professionals confirming a woman’s eligibility for the trial do not need to be on delegation log. However, the discussion should be documented in the woman’s pregnancy notes and the doctor’s details should be recorded on REDCap*

- Ensure site file remains up-to-date throughout the trial
  - Add new documents to site file
  - Label historical documents ‘superseded’ and the date superseded

Green Light

Sites are required to have the following in place in order to receive the ‘Green Light’:

- ✓ SIV taken place
- ✓ Local trust capability and capacity
- ✓ CV & GCP sent to BCTU
- ✓ Delegation log completed
- ✓ PI signature in the protocol
- ✓ Site agreement fully signed

Study support

giant-panda@trials.bham.ac.uk

0121 414 3902 ***(Mon-Fri, 9-5pm)***

Regular

Monthly

zoom

Any questions?

Appendix

Giant PANDA summary

Funder:	Sponsor:	Coordinating centre:
NIHR | National Institute for Health Research HTA	University of Birmingham	BCTU Birmingham Clinical Trials Unit

Approvals:

London - South East Research Ethics Committee – *3rd November 2020*

Medicines and Healthcare products Regulatory Agency – *16th December 2020*

Health Research Authority – *17th December 2020*

Reference numbers:

EudraCT number 2020-003410-12

ISRCTN reference number ISRCTN12792616

IRAS reference number 284958

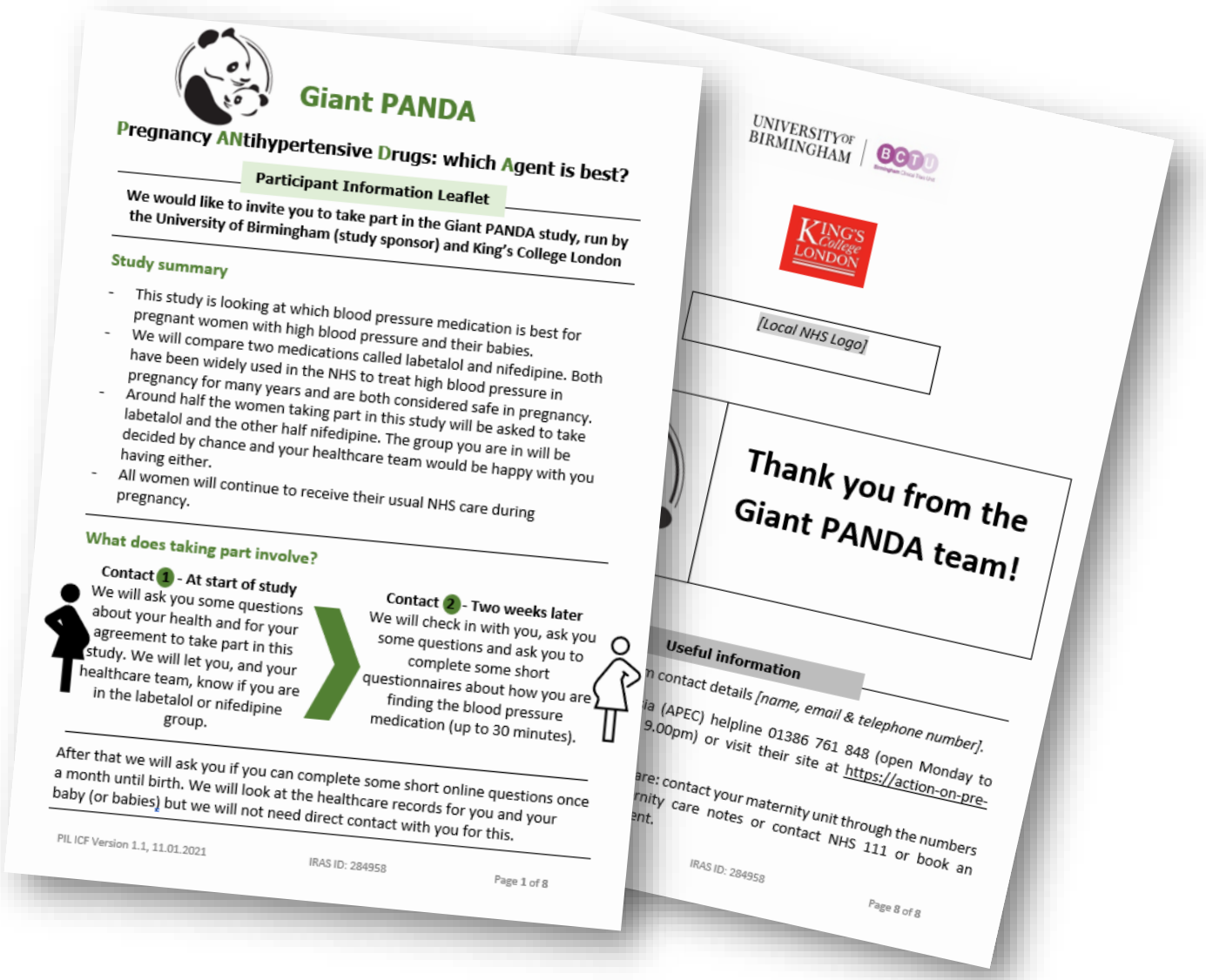
Amendments:

1 - Non-substantial – NSA_01 - *19th January 2021*

Protocol version & date: *version 1.1, 11th January 2021*

Participant facing documents

Participant Information Leaflet



Giant PANDA

Pregnancy ANtihypertensive Drugs: which Agent is best?

Participant Information Leaflet

We would like to invite you to take part in the Giant PANDA study, run by the University of Birmingham (study sponsor) and King's College London

Study summary

- This study is looking at which blood pressure medication is best for pregnant women with high blood pressure and their babies.
- We will compare two medications called labetalol and nifedipine. Both have been widely used in the NHS to treat high blood pressure in pregnancy for many years and are both considered safe in pregnancy.
- Around half the women taking part in this study will be asked to take labetalol and the other half nifedipine. The group you are in will be decided by chance and your healthcare team would be happy with you having either.
- All women will continue to receive their usual NHS care during pregnancy.

What does taking part involve?

Contact 1 - At start of study
We will ask you some questions about your health and for your agreement to take part in this study. We will let you, and your healthcare team, know if you are in the labetalol or nifedipine group.

Contact 2 - Two weeks later
We will check in with you, ask you some questions and ask you to complete some short questionnaires about how you are finding the blood pressure medication (up to 30 minutes).

After that we will ask you if you can complete some short online questions once a month until birth. We will look at the healthcare records for you and your baby (or babies) but we will not need direct contact with you for this.

PIL ICF Version 1.1, 11.01.2021 IRAS ID: 284958 Page 1 of 8

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[Local NHS Logo]

Thank you from the Giant PANDA team!

Useful information

...n contact details *[name, email & telephone number]*.
...ia (APEC) helpline 01386 761 848 (open Monday to ...9.00pm) or visit their site at https://action-on-pre-
...are: contact your maternity unit through the numbers ...rnity care notes or contact NHS 111 or book an ...ent.

IRAS ID: 284958 Page 8 of 8

- Participant Information Leaflet and Informed Consent Form are 1 document (8 A5 pages)
- Participant Information Leaflet needs to be localised with the trusts logo and PALs information

Informed consent

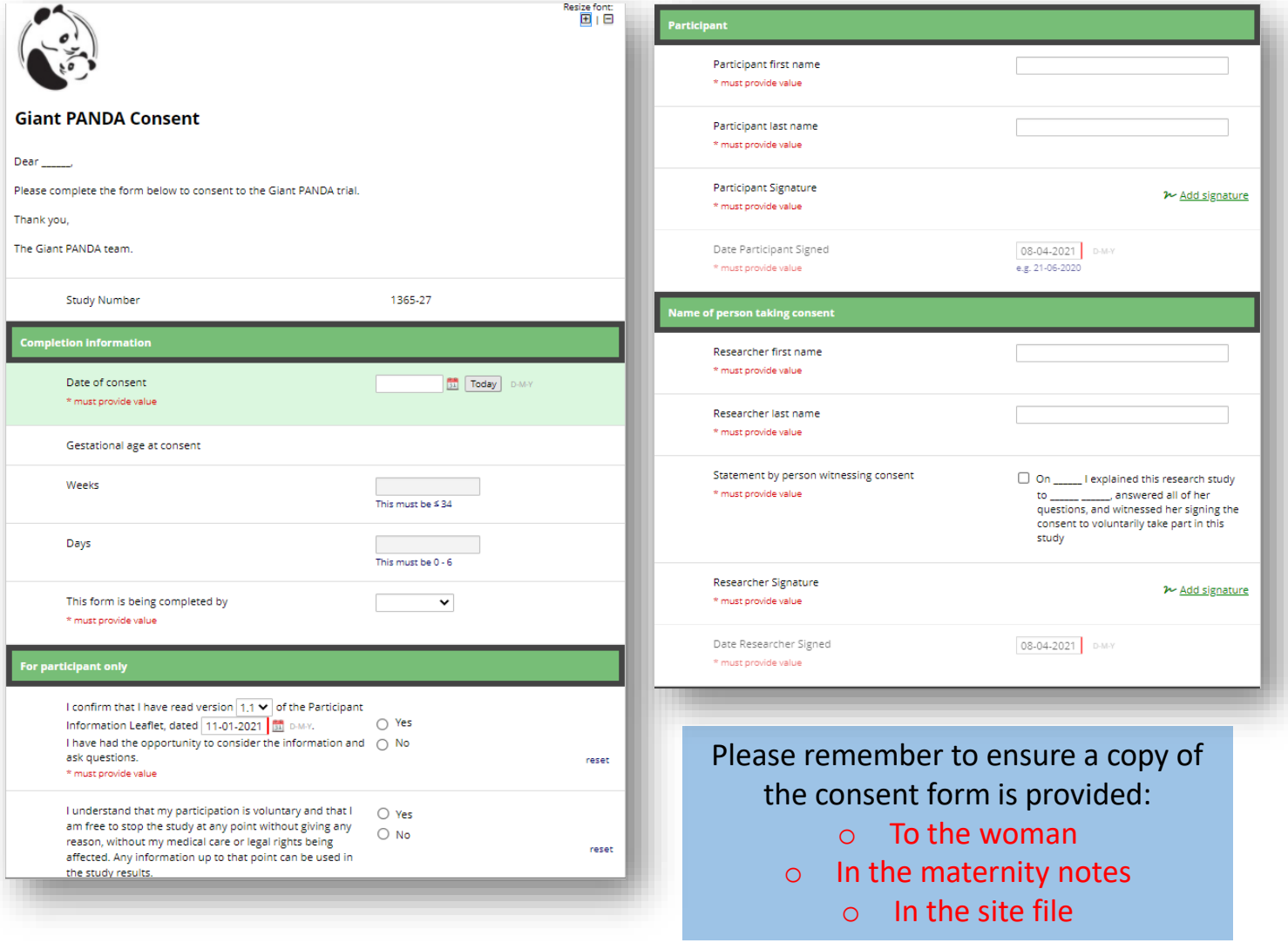
- Women should be provided with a study PIL in advance of their decision to participate or not
- Women should be asked if they have any questions about the study

The discussion about consent to the study should cover the **following key points**:

- Ensure the woman has had time to ask any questions they may have
- Ensure they understand that taking part in voluntary & they are free to stop the study at any point & their decision to take part will not affect current or future NHS treatment
- Ensure they understand that we will be collecting data about them and their baby(ies) over their pregnancy until up to 28 days after delivery birth. This data will be shared with members of the research team where it is relevant to them taking part but anyone who sees this data is bound by strict confidentiality rules.
- Ensure they understand their data maybe used to support future research but will be shared anonymously so no individual can be identified
- Ensure they understand their data will be stored securely for up to 25 years
- Ensure they understand that the Giant PANDA study is trying to work out which blood pressure medication in pregnancy works best. They understand that we are doing this within a trail by deciding which medication they will get at random by a computer (like tossing a coin) and then that medication will be prescribed in the usual way by the doctors looking after them

Consent form

CRF 2 – Consent form



Resize font:

Giant PANDA Consent

Dear _____,

Please complete the form below to consent to the Giant PANDA trial.

Thank you,

The Giant PANDA team.

Study Number 1365-27

Completion Information

Date of consent
* must provide value
Today D-M-Y

Gestational age at consent

Weeks
This must be ≤ 34

Days
This must be 0 - 6

This form is being completed by
* must provide value

For participant only

I confirm that I have read version 1.1 of the Participant Information Leaflet, dated 11-01-2021 D-M-Y. ○ Yes ○ No

I have had the opportunity to consider the information and ask questions. reset
* must provide value

I understand that my participation is voluntary and that I am free to stop the study at any point without giving any reason, without my medical care or legal rights being affected. Any information up to that point can be used in the study results. ○ Yes ○ No reset

Participant

Participant first name
* must provide value

Participant last name
* must provide value

Participant Signature
* must provide value
Add signature

Date Participant Signed
* must provide value
08-04-2021 D-M-Y
e.g. 21-06-2020

Name of person taking consent

Researcher first name
* must provide value

Researcher last name
* must provide value

Statement by person witnessing consent
* must provide value
☐ On _____ I explained this research study to _____ _____, answered all of her questions, and witnessed her signing the consent to voluntarily take part in this study

Researcher Signature
* must provide value
Add signature

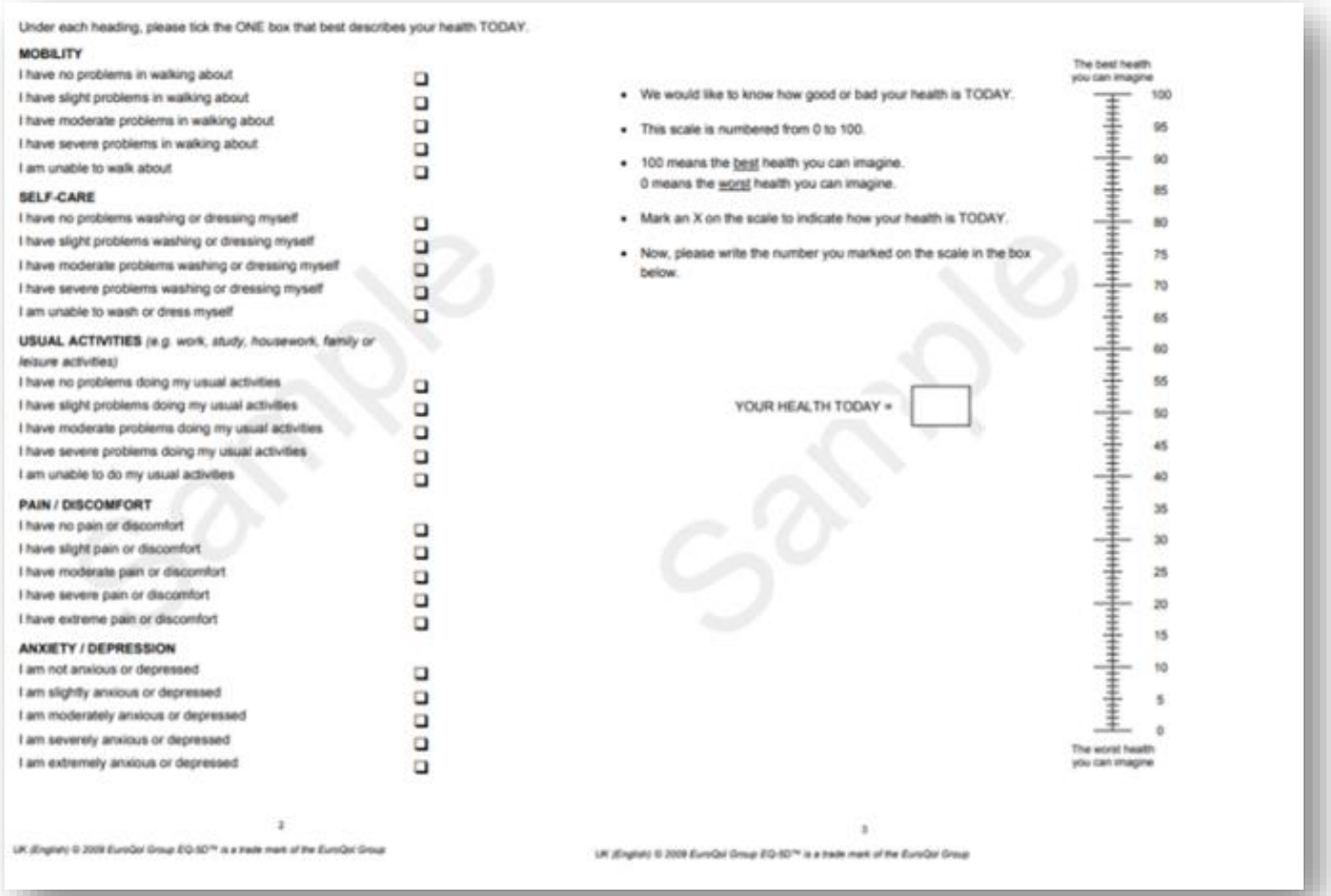
Date Researcher Signed
* must provide value
08-04-2021 D-M-Y

Please remember to ensure a copy of the consent form is provided:

- To the woman
- In the maternity notes
- In the site file

- For participation **ALL** women need to agree to **statements 1-6 & sign/date** the consent form
- For **trial participation** women need to agree to **statement 7**
- Statements 8,9 & study results are **optional**
- If written consent is provided each box must be initialled
- Only midwives or clinicians on the delegation log can consent participants

EQ-5D (at baseline)



Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY
- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE
- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

2

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health you can imagine
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
The worst health you can imagine

3

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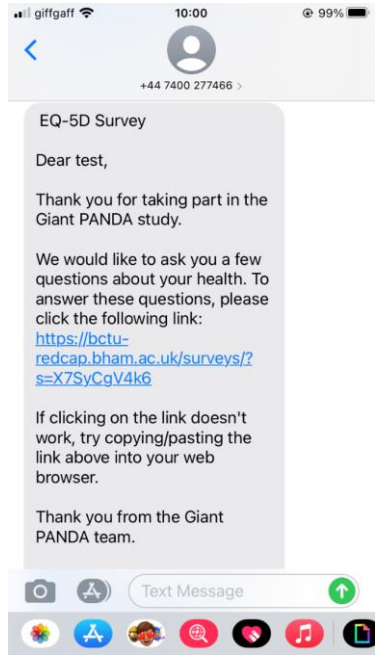
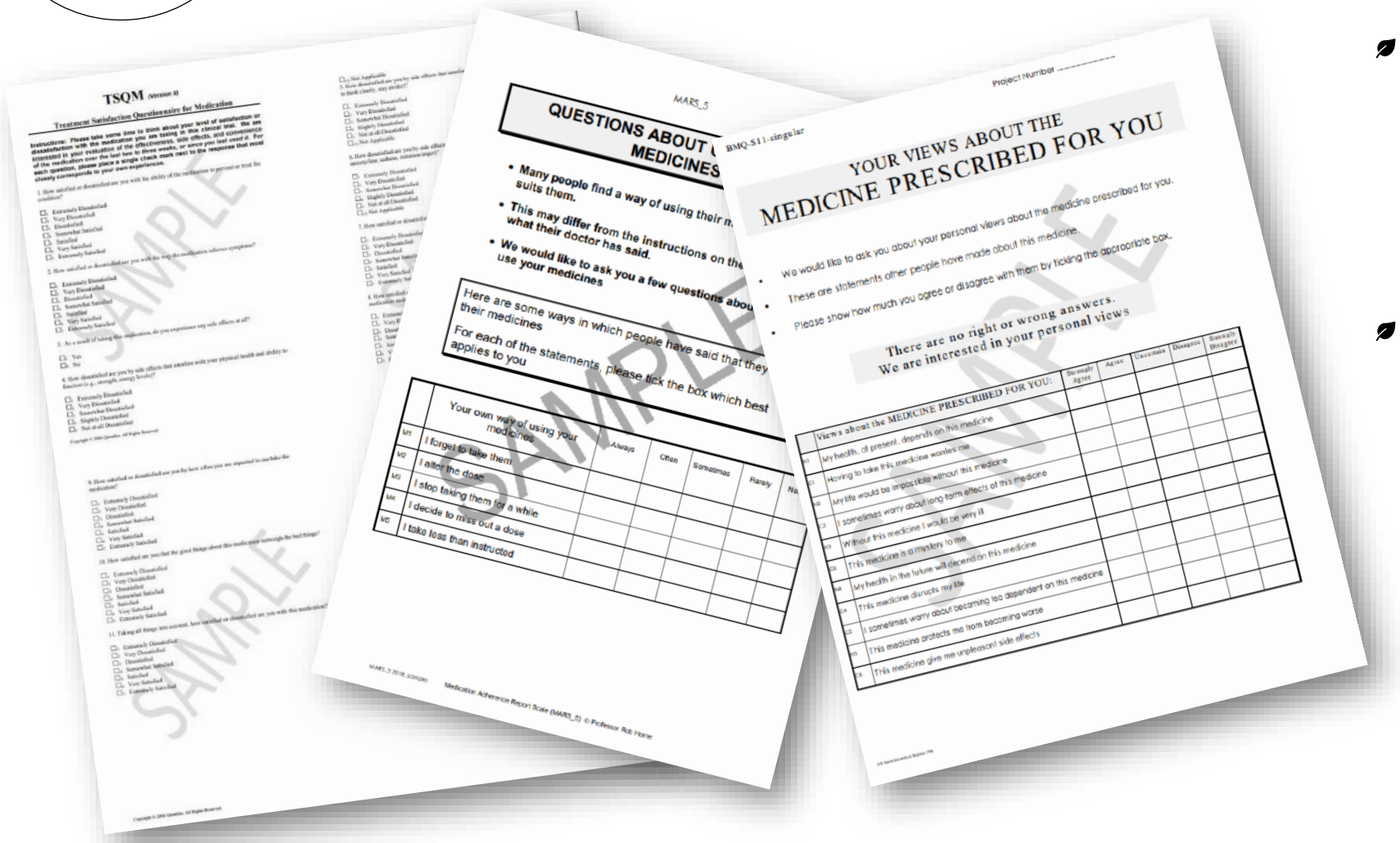
Sample Sample

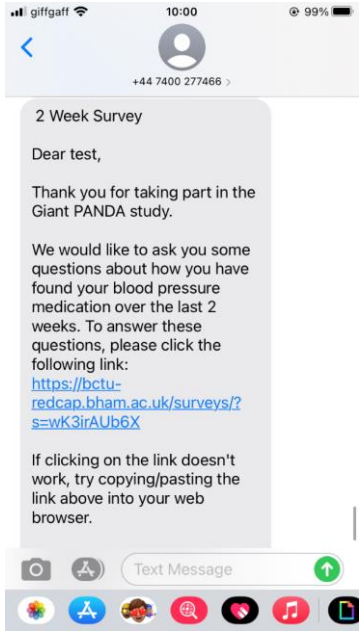
- Following consent all women are asked to complete an EQ-5D survey
- A link to this survey will be texted to participating women
- Please ensure women complete this before they are randomised



Two Week Contact survey

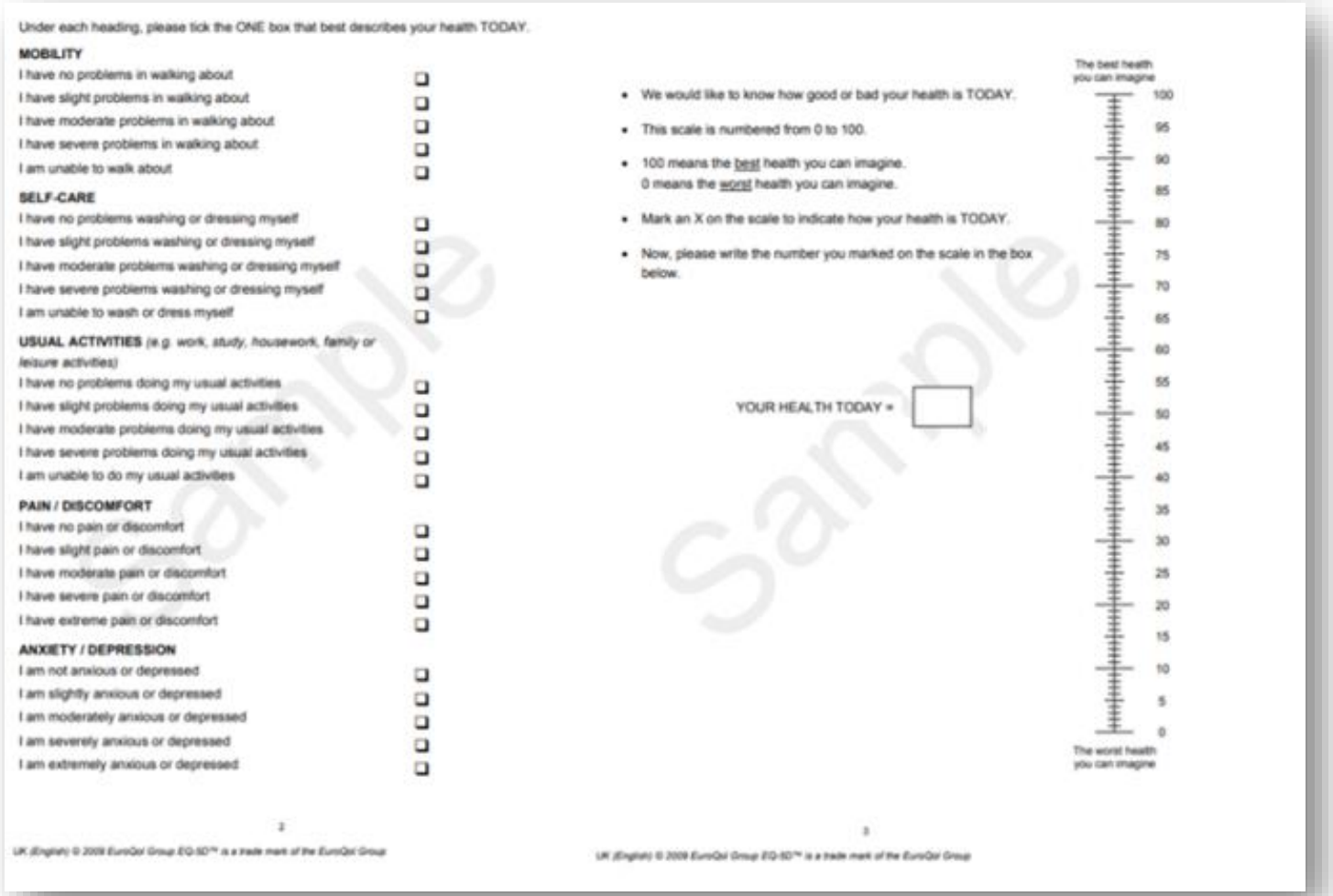


- All women will be asked to complete a survey at 2 weeks after randomisation (for trial participants) or after consent (for observational participants)
- A link to this survey will be texted to participating women



Please remind women about the 4 weekly contact survey thereafter

Four Week Contact survey



Under each heading, please tick the ONE box that best describes your health TODAY.

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- I am unable to walk about

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- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT
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- I have severe pain or discomfort
- I have extreme pain or discomfort

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- I am severely anxious or depressed
- I am extremely anxious or depressed

2

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

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- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health you can imagine
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
The worst health you can imagine

3

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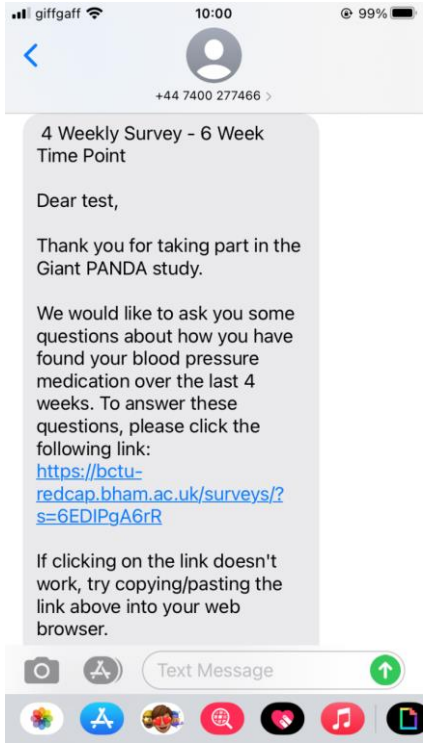
Sample Sample

- All women will be asked to complete a survey every 4 weeks
- A link to this survey will be texted to participating women



Midwife completed e-CRFs

e-CRFs – Midwife completed

- eCRFs to be completed before randomisation
  - Screening & Eligibility
  - Maternal Details (pre-randomisation)

PLUS the randomisation eCRF 's if the woman is participating in the trial

- eCRFs to be completed after discharge
  - Maternal Details (post-randomisation)
  - Antenatal Outpatient Preliminary & Contacts
  - Antenatal Inpatient Preliminary & Contacts (including admission for birth)
  - Antenatal scans
  - Maternal outcomes
  - Neonatal outcomes

- eCRFs to be completed as needed
  - Protocol Deviation
  - SAE (CTIMP)
  - Change of Status