



**PROTECT**



Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

# **WP4: The PROTECT Pregnancy Study**

## **New tools for data collection from consumers**

PROTECT Final Symposium

European Medicines Agency, London

18-20<sup>th</sup> February 2015

Nancy Dreyer. Shahrul Mt-Isa & Stella Blackburn on behalf of WP4

## **PROTECT WP4:**

### **New methods of pharmacovigilance**

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“The PROTECT project has received support from the Innovative Medicines Initiative Joint Undertaking ([www.imi.europa.eu](http://www.imi.europa.eu)) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.”

## WP 4 Active Participants

<b>Nancy Dreyer</b>	Quintiles- WPL
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<b>Stella Blackburn</b>	Quintiles (WPL 2009-14)
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<b>Lynne Comiskey</b>	Genzyme- Proj. Mgr
<b>Maja Laursen</b>	Staten Serum Institut
<b>Llokje de Jong-van den Berg, Priscilla Zetstra</b>	University of Groningen
<b>Simon Thomas, Luke Richardson, Sally Stephens</b>	University of Newcastle
<b>Rebecca Johnson</b>	IAPO
<b>Shahrul Mt-Isa, Christine Hallgreen, Deborah Ashby</b>	Imperial College
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<b>Jens Peter Balling</b>	Lundbeck (WPL 2009-2013)
<b>Alison Bourke</b>	THIN
<b>Pfizer</b>	Financial Support
<b>GSK</b>	Logistics Support

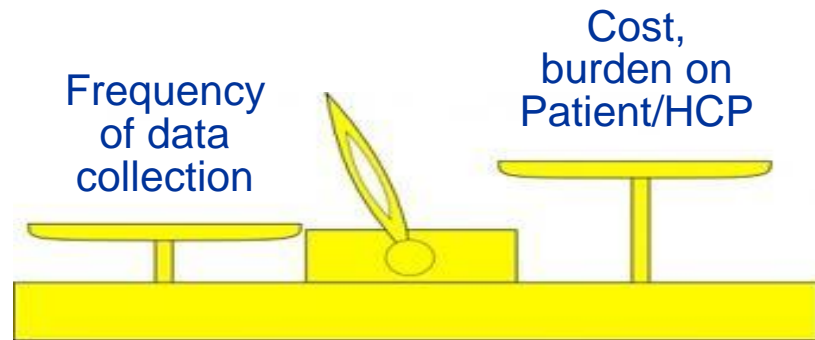
## The Issue

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- Diseases do not disappear just because a woman is pregnant
- A woman often does not realise she is pregnant until she misses a period
- Critical period of organogenesis is from 15-60 days post conception
- Estimated 84-99% of women take a prescription medicine at some time during pregnancy
- Women may change to herbal or homeopathic medicines in the belief that they are “natural” and somehow safer



# Examples of methods for data collection



Electronic health records



Dispensing records



## New tools for data collection from consumers

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### **An exploratory study of self-reported medication use in pregnant women and pregnancy outcomes**

#### Objectives

To assess the extent to which data collected directly from pregnant women via the Internet and IVRS provides information on medication use and other potential risk factors throughout pregnancy, and is suitable for research purposes



## An exploratory study of self-reported medication use in pregnant women and pregnancy outcomes

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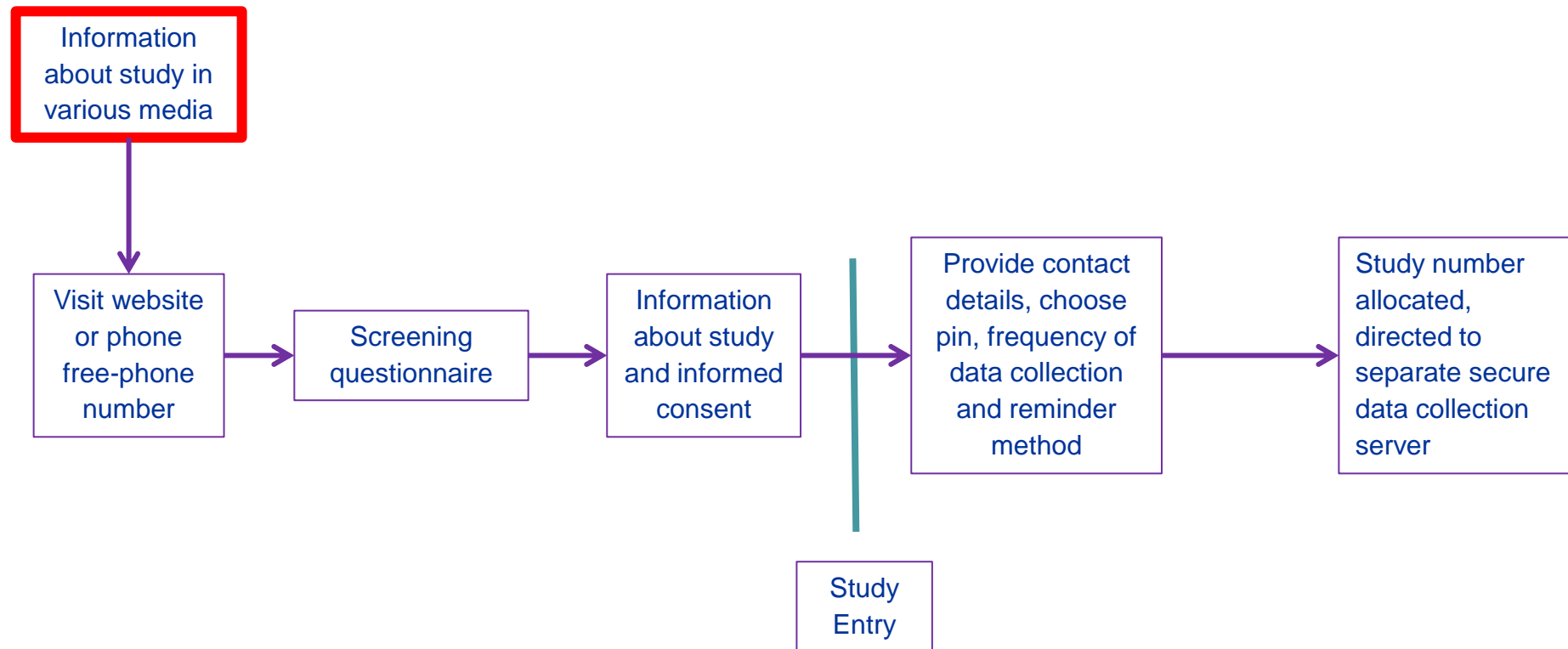
### Questions:

- Can we get data earlier in pregnancy than traditional routes?
- How consistently and for how long will women provide the data requested?
- How representative are the women?
- How important are data *not* captured by EHR or pharmacy databases?
- Is the information of sufficient quality to be used for pharmacovigilance?





# Study entry process



## Examples of the media used to advertise the study



## Entry website



### Welcome

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium



***PROTECT Pregnancy study***  
Click on this flag if you live in the UK and you would like to learn more about our study.



***PROTECT Zwangerschap studie***  
Klik op deze vlag indien u in Nederland woont en meer te weten wilt komen over onze studie.



***PROTECT Graviditetsstudie***  
Klik på dette flag hvis du bor i Danmark og gerne vil vide mere om studiet



***PROTECT Projekt badawczy dla kobiet w ciąży***  
Jeśli mieszka Pani w Polsce i chciałaby otrzymywać dodatkowe informacje na temat projektu proszę kliknąć na flagę.







The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking ([www.imi.europa.eu](http://www.imi.europa.eu)) under grant agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.  
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» Til startside

Velkommen fra det danske studieteam i graviditetsstudiet PROTECT.

STATENS  
SERUM  
INSTITUT



Sundhedsstyrelsen

Maja og hendes kollegaer i Sundhedsstyrelsen/Statens Serum Institut står for rekrutteringen af deltagere i Danmark og for de forskellige lovgivningsmæssige og etiske godkendelser, der er nødvendige, før forskningen kan gå i gang.

Maja mener, at vi i Danmark har fremragende registre med detaljerede oplysninger om salget af receptpligtig medicin på individuelt niveau og om spædbørnenes helbred ved fødslen. Vi mangler dog oplysninger om, hvorvidt medicin, der er ordineret, rent faktisk tages. Desuden er det kun den gravide kvinde selv, der kan give information om anvendelsen af receptfri medicin, naturlægemidler og kosttilskud. Dette studie vil desuden give os oplysninger om, hvorvidt det er muligt at rekruttere kvinderne direkte fra internettet; en metode, vi antager vil blive brugt i fremtiden. I så vil derfor ondfordre dig til at deltage.

» Powrót do strony głównej

Pozdrowienia od polskiego zespołu badawczego realizującego badanie dotyczące kobiet w ciąży PROTECT!



Serdecznie witamy w projekcie PROTECT. Jesteśmy pracownikami Katedry i Zakładu Genetyki Medycznej Uniwersytetu Medycznego w Poznaniu i od wielu lat prowadzimy projekty badawcze dotyczące czynników mających znaczenie dla rozwoju dziecka – zarówno w okresie prenatalnym, jak i po urodzeniu, a także uczestniczymy w podobnych projektach międzynarodowych. Dla projektu PROTECT uzyskaliśmy wszystkie niezbędne zezwolenia, w tym zgodę komisji bioetycznej.

Ta część projektu PROTECT, w której uczestniczymy, dotyczy opracowania zupełnie nowych metod uzyskiwania informacji o przebiegu ciąży – za pomocą Internetu i bezpośrednio od kobiet. Liczymy na to, że dane te będą wysokiej jakości i jeśli metoda się sprawdzi, w przyszłości przyczyni się do poprawy opieki medycznej nad kobietami w ciąży.

Dane będą zbierane w Polsce, Wielkiej Brytanii, Holandii i Danii. Nasz Zespół odpowiedzialny jest rekrutację polskiej grupy kobiet w ciąży. Serdecznie zapraszamy do włączenia się do tych ważnych badań, a także prosimy o pomoc w rozpowszechnieniu informacji o PROTECT wśród

» Terug naar Home

Welkom namens het Nederlandse onderzoeksteam van het PROTECT zwangerschapsonderzoek.



Van links naar rechts: Lolkje T. W. de Jong-van den Berg, Priscilla Zetstra-van der Woude, Sipke Visser

Lolkje en haar collega's van de afdeling Farmaco-epidemiologie aan de Universiteit van Groningen nemen de leiding bij het werven van deelnemers in Nederland en bij het aanvragen van toestemming die nodig is voordat het onderzoek kan plaatsvinden.

Lolkjes motivatie is dat vrouwen die tijdens de zwangerschap geneesmiddelen moeten gebruiken, vanwege chronische ziektes, het verdienen om goed geïnformeerd te worden over risico's en voordelen van geneesmiddelen die zij gebruiken. Voor onderzoek hiernaar hebben we goede en juiste informatie nodig over geneesmiddelen die tijdens de zwangerschap

» Return Home

Hello from the UK Study Team for the PROTECT Pregnancy study.

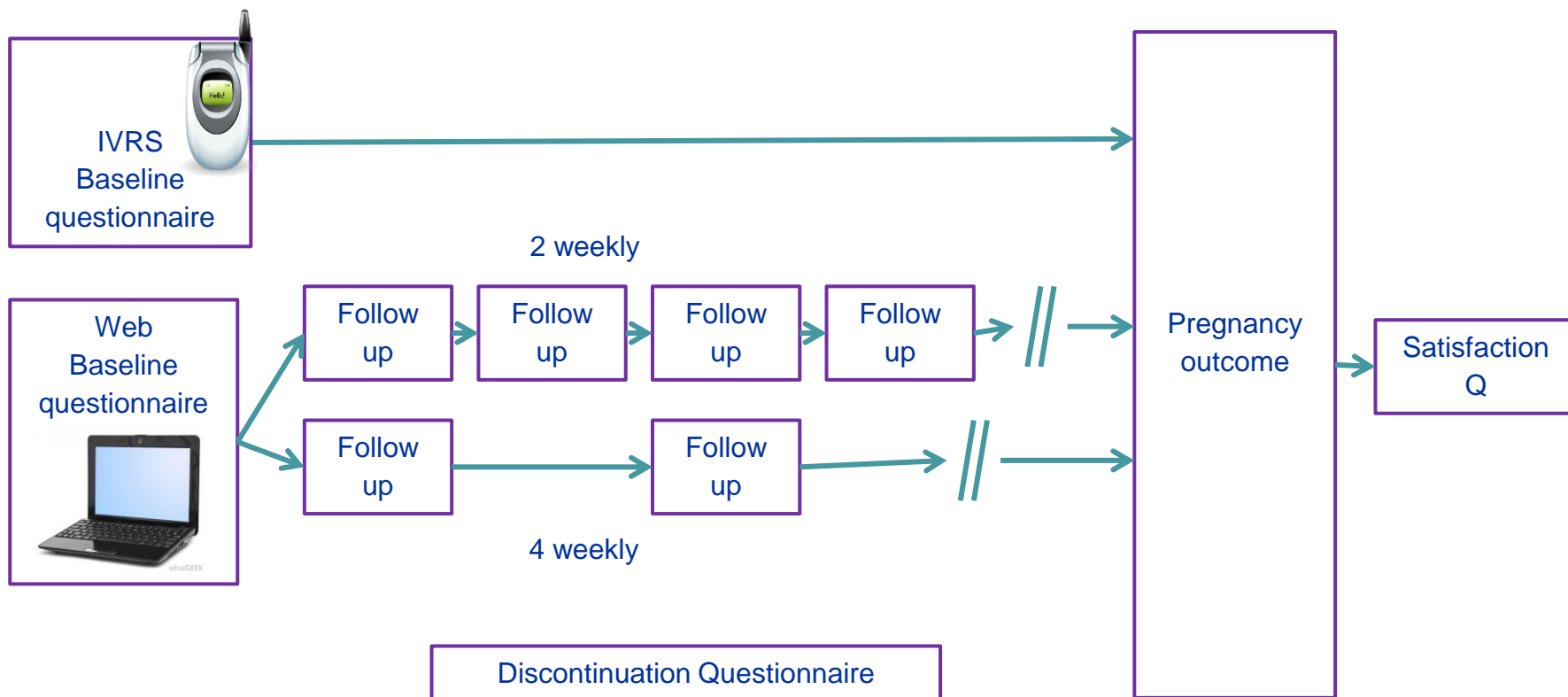


Pictured L-R: Sally Stephens, Simon Thomas, Luke Richardson

Simon and colleagues in the UK Teratology Information Service are taking the lead for participant recruitment in the UK and for the various regulatory and ethical approvals that are needed before the research can take place.

Simon feels that as an increasing number of women need to use medicines during pregnancy to treat conditions that arise after they become pregnant or for management of longstanding medical problems starting before pregnancy. It is important that information on the safety of medicines use during pregnancy is collected as efficiently as possible so that any safety concerns can be identified as soon as possible and that women can be given accurate information on the risks and benefits of medicines use. Pregnant women taking medicines can provide unique and essential information, including the medicines they have taken and about any health issues affecting their baby. This study is essential for developing methods collecting this information and I would encourage pregnant women to participate in it.

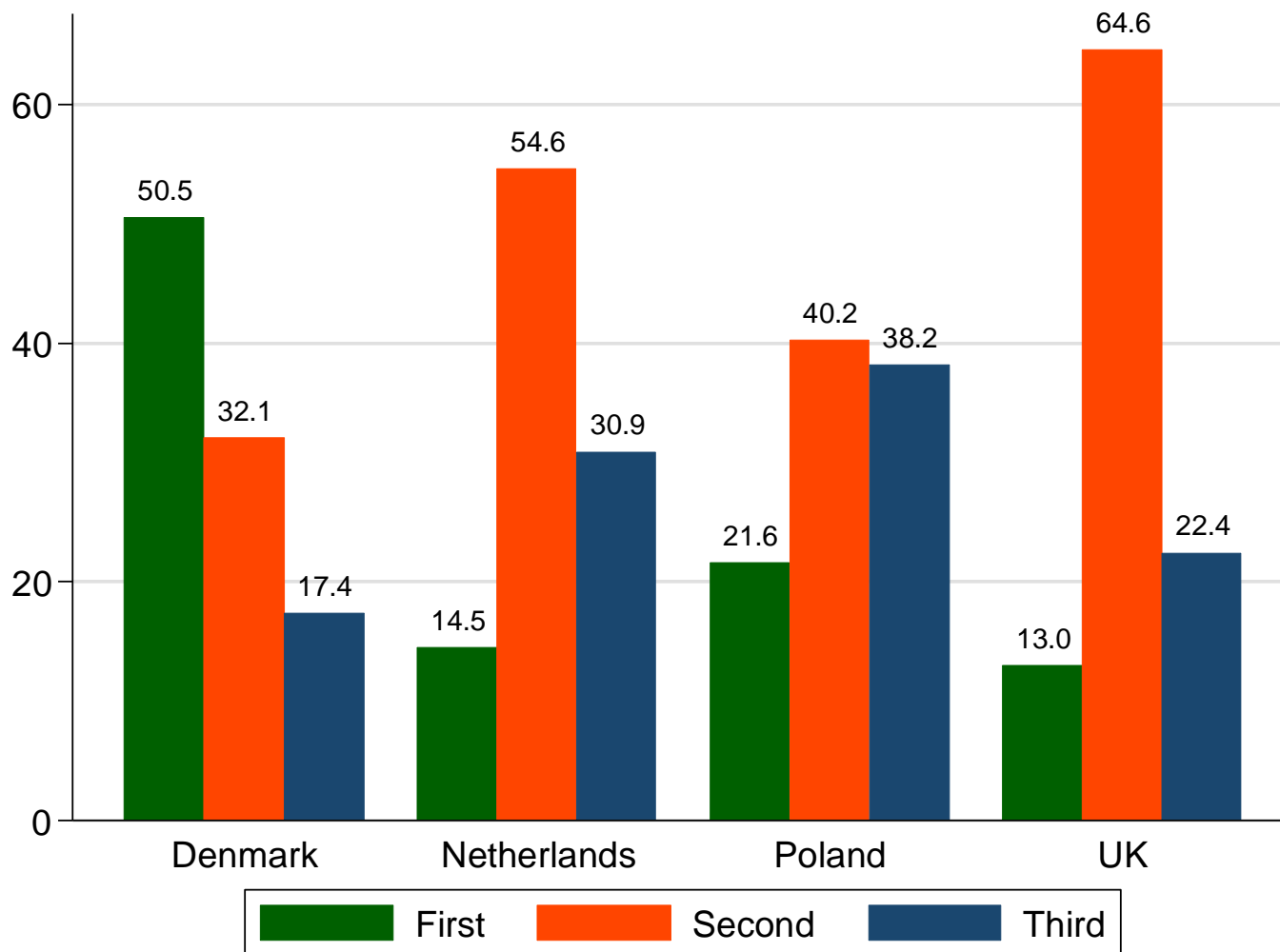
# Data collection flow



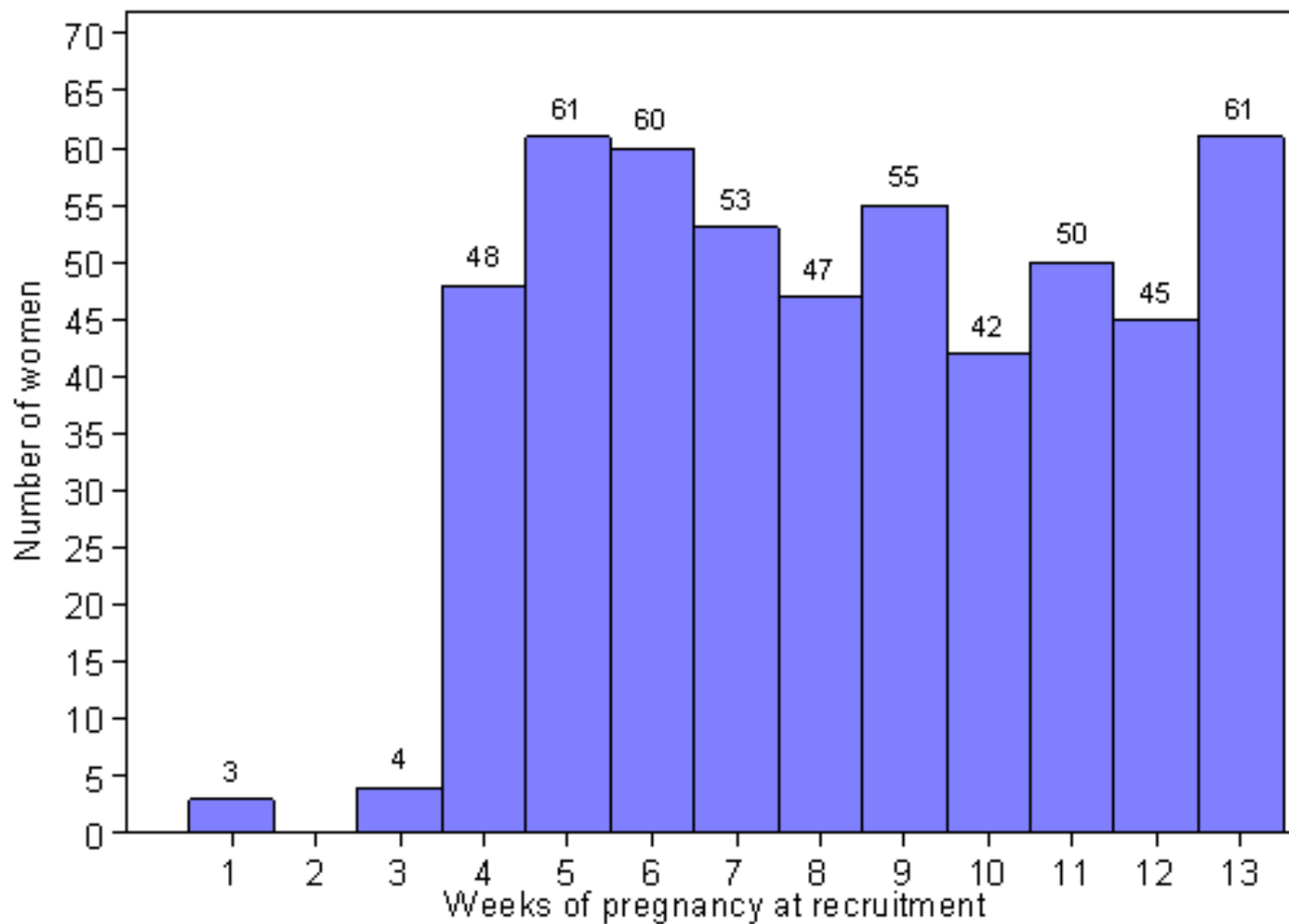
Can we get the data early in pregnancy?



## Enrollment by trimester (N=2065)



## Enrollment during first trimester (N=529)





## PROTECT Recruitment Methods, Costs & Yield

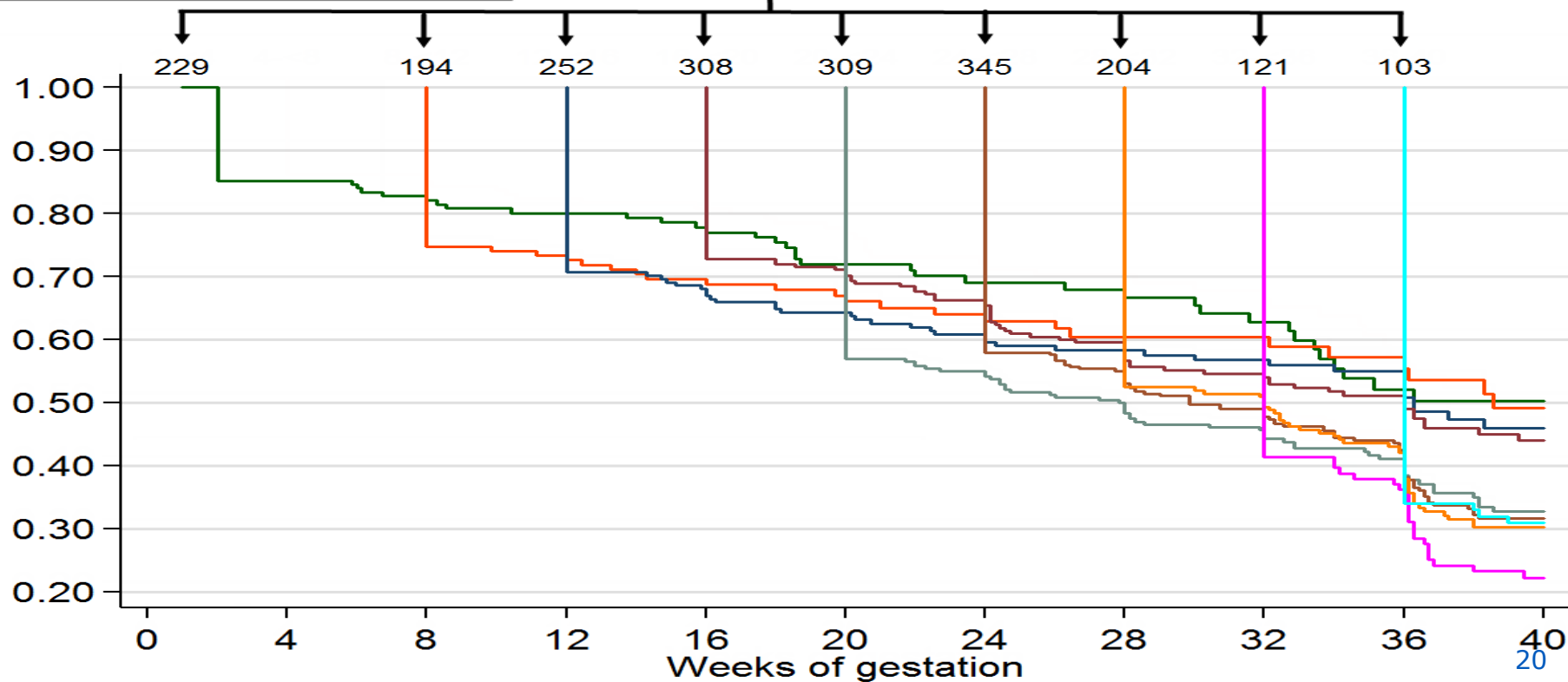
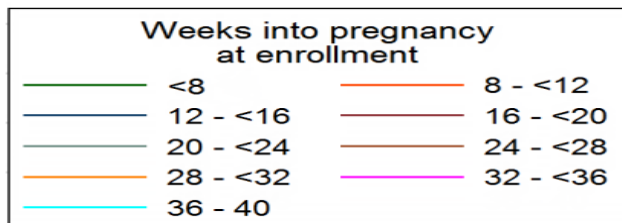
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Method	Number Recruited	Cost (€) per Recruit
Paid Website Advertisements	671	25
Email List Rentals	995	23
Leaflets in Pharmacies	194	83
Paid Social Media (Facebook Ad)	1	186
Total Recruited by Paid Methods	1867	30
Total Recruited by Unpaid Methods*	195	
<b>Total Recruited</b>	<b>2062</b>	

\*Includes 3 recruited from *unpaid* website advertisements

How consistently will  
respondents report and  
for how long?



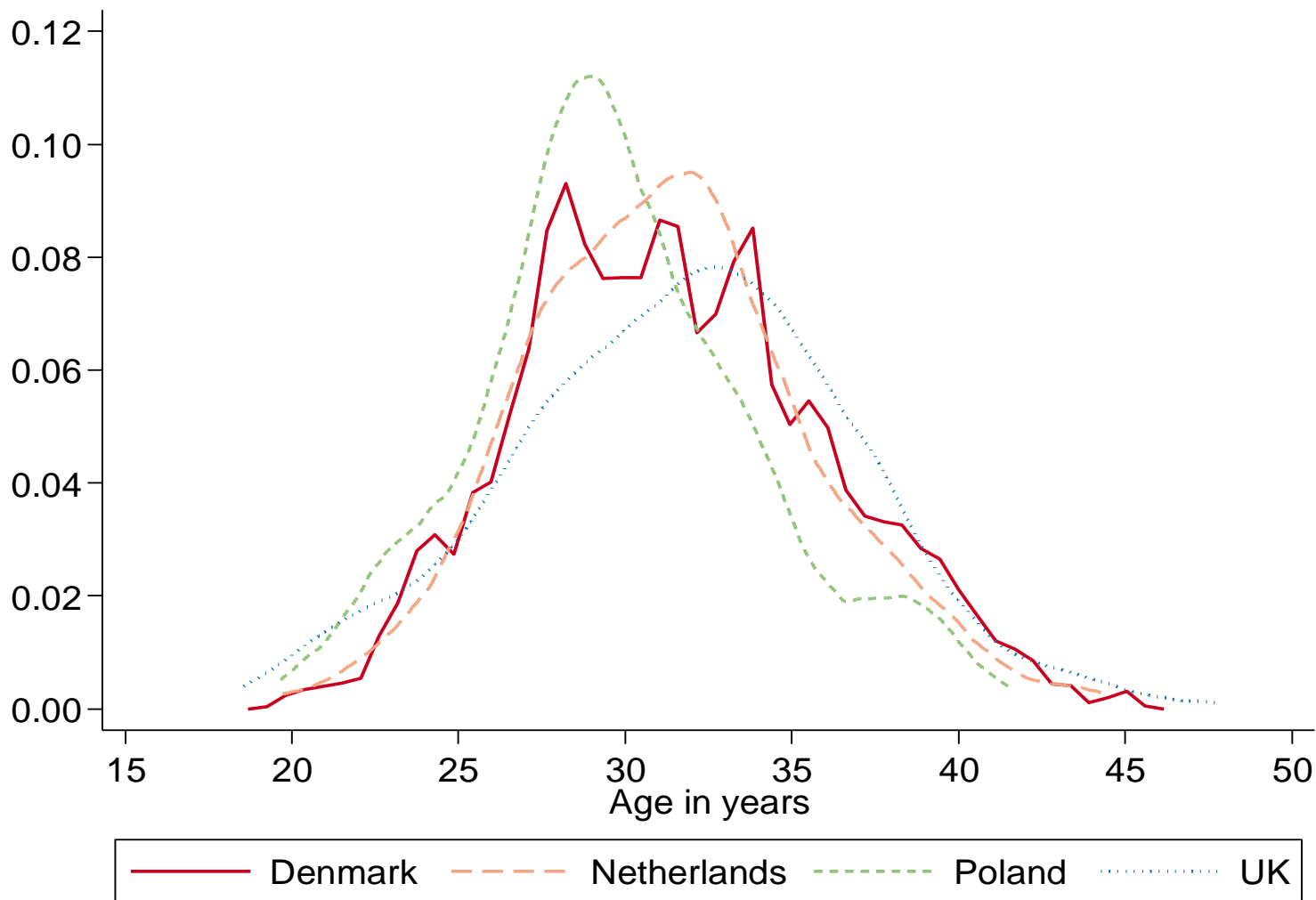


## Women lost before baseline

	DK	NL	PL	UK	Total
Number of questionnaires sent	119	76	27	137	<b>358</b>
Number of replies (% of sent)	24 (20)	13 (17)	1 (4)	9 (7)	<b>47 (13)</b>
Reasons					
I was no longer interested in the study	1	1	0	0	<b>2</b>
The questionnaire was too long	3	1	0	2	<b>6</b>
The commitment required was too burdensome	2	2	0	0	<b>4</b>
The questions were too difficult	0	0	0	0	<b>0</b>
The questions were too personal	0	0	0	0	<b>0</b>
I was no longer pregnant	6	1	0	0	<b>7</b>
Other	16	9	1	8	<b>34</b>

# Demographics of the PROTECT population

## Age at end of pregnancy



## Height, weight and BMI

	DK	NL	PL	UK
Weight before pregnancy, mean (SD) kg	70.1 (14.6)	70.7 (12.9)	62.6 (11.7)	71.6 (17.6)
Height, mean (SD) cm	169.3 (6.7)	170.6 (9.2)	166.6 (6.2)	164.8 (13.7)
BMI, mean (SD)	24.4 (4.7)	24.6 (9.1)	22.5 (3.6)	27.4 (13.2)
BMI	%, (no.)	%, (no.)	%, (no.)	%, (no.)
<18	2.2 (14)	0.4 (2)	4.6 (11)	2.0 (14)
18 - <25	62.9 (402)	63.9 (304)	75.5 (182)	50.8 (360)
25 - <30	22.8 (146)	27.1 (129)	12.4 (30)	23.3 (165)
30 - <35	8.5 (54)	6.9 (33)	2.9 (7)	12.6 (89)
≥35	3.6 (23)	1.7 (8)	1.2 (3)	9.9 (70)
Missing	0.0 (0)	0.0 (0)	3.3 (8)	1.6 (11)

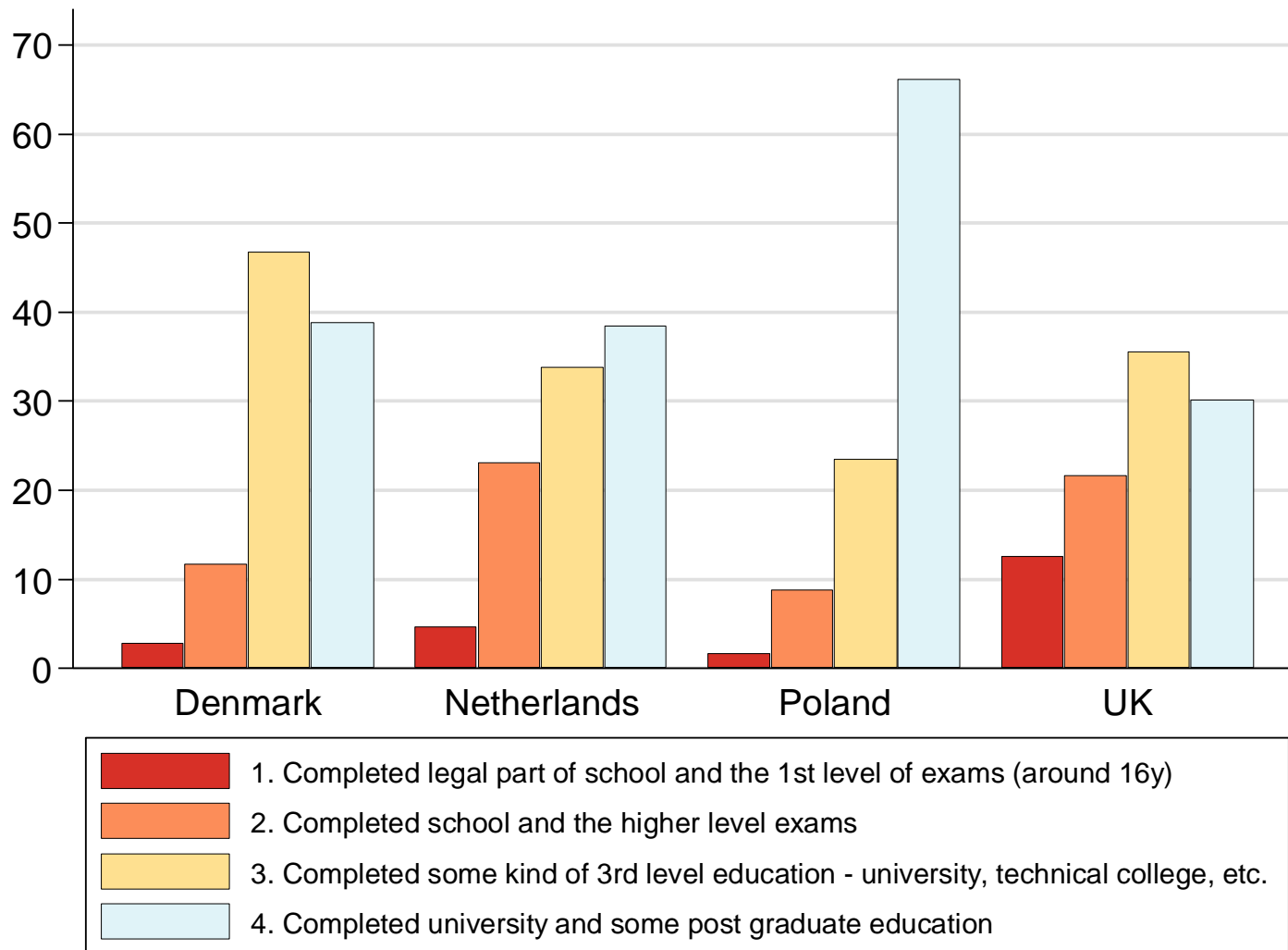
## Ethnic origin of PROTECT population

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<b>Ethnic Group</b>	<b>DK (%)</b>	<b>NL (%)</b>	<b>PL (%)</b>	<b>UK (%)</b>
Asian or Chinese	0.8	1.3	0.0	2.5
Black	0.3	0.0	0.0	0.9
Mixed	1.7	1.7	0.0	1.3
Other Ethnic	0.5	0.4	0.0	0.1
White	96.2	95.8	99.6	95.0
Unknown/ Missing	0.5	0.8	0.4	0.7



# Education by Country



## Current pregnancy and gravidity

	DK	NL	PL	UK
First pregnancy	38.3% (245)	47.3% (225)	50.6% (122)	41.6% (295)

### Outcomes: median (range) from previous pregnancies

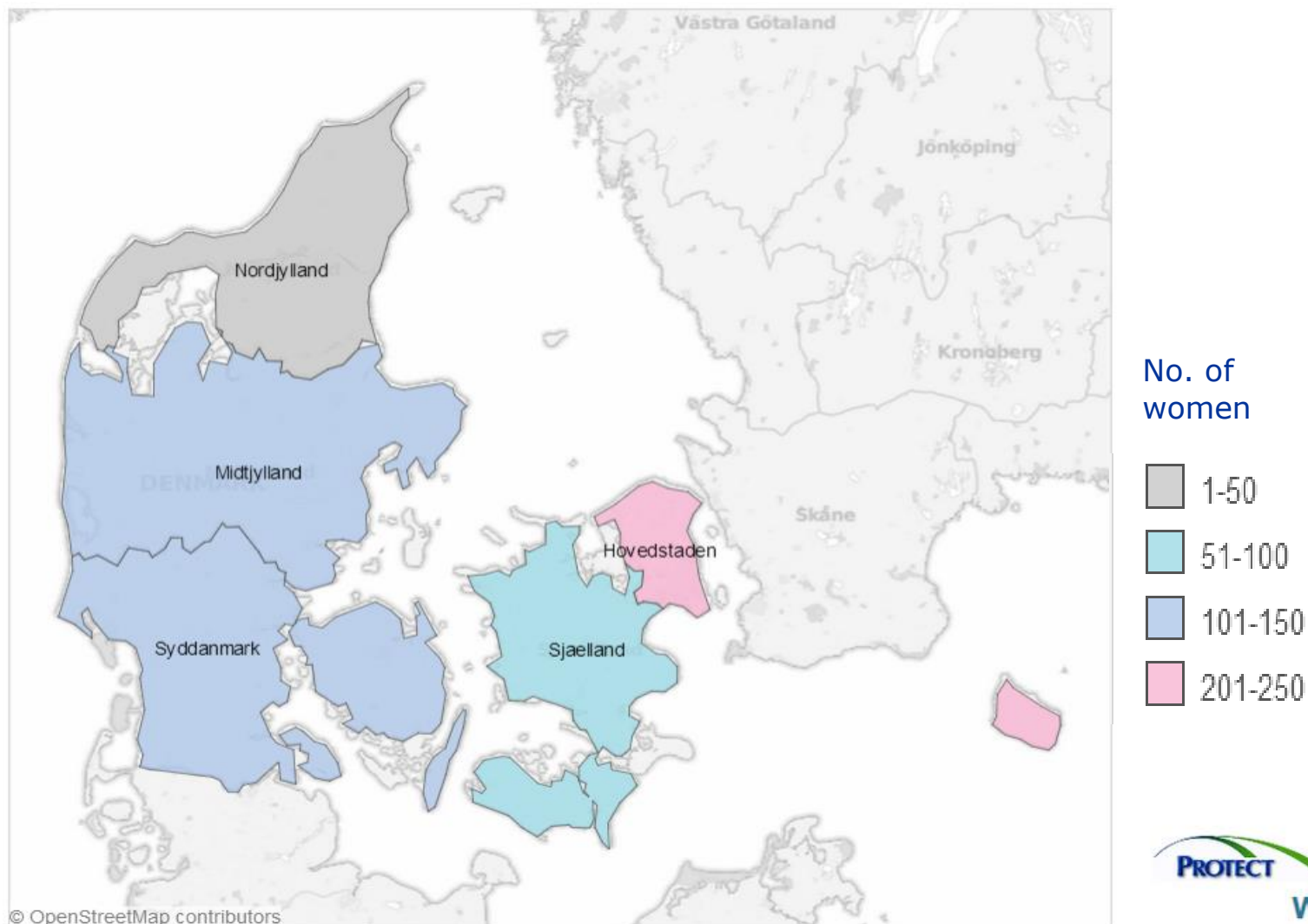
	DK	NL	PL	UK
Number of previous pregnancies	1 (1 - 12)	1 (1 - 13)	1 (1 - 5)	2 (1 - 12)
Live birth	1 (0 - 5)	1 (0 - 4)	1 (0 - 3)	1 (0 - 9)
Miscarriage	1 (0 - 10)	1 (0 - 13)	1 (0 - 3)	1 (0 - 11)
Elective termination	1 (0 - 4)	1 (0 - 2)	1 (0 - 1)	1 (0 - 3)
Stillbirth	1 (0 - 1)	1 (0 - 1)	1 (0 - 1)	1 (0 - 1)
Ectopic	1 (0 - 1)	1 (0 - 1)	1 (0 - 1)	1 (0 - 1)

# Are these results generalisable?

[How representative are the women?]



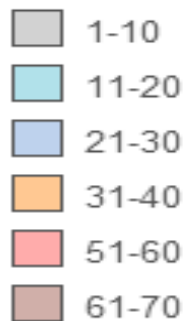
# Denmark

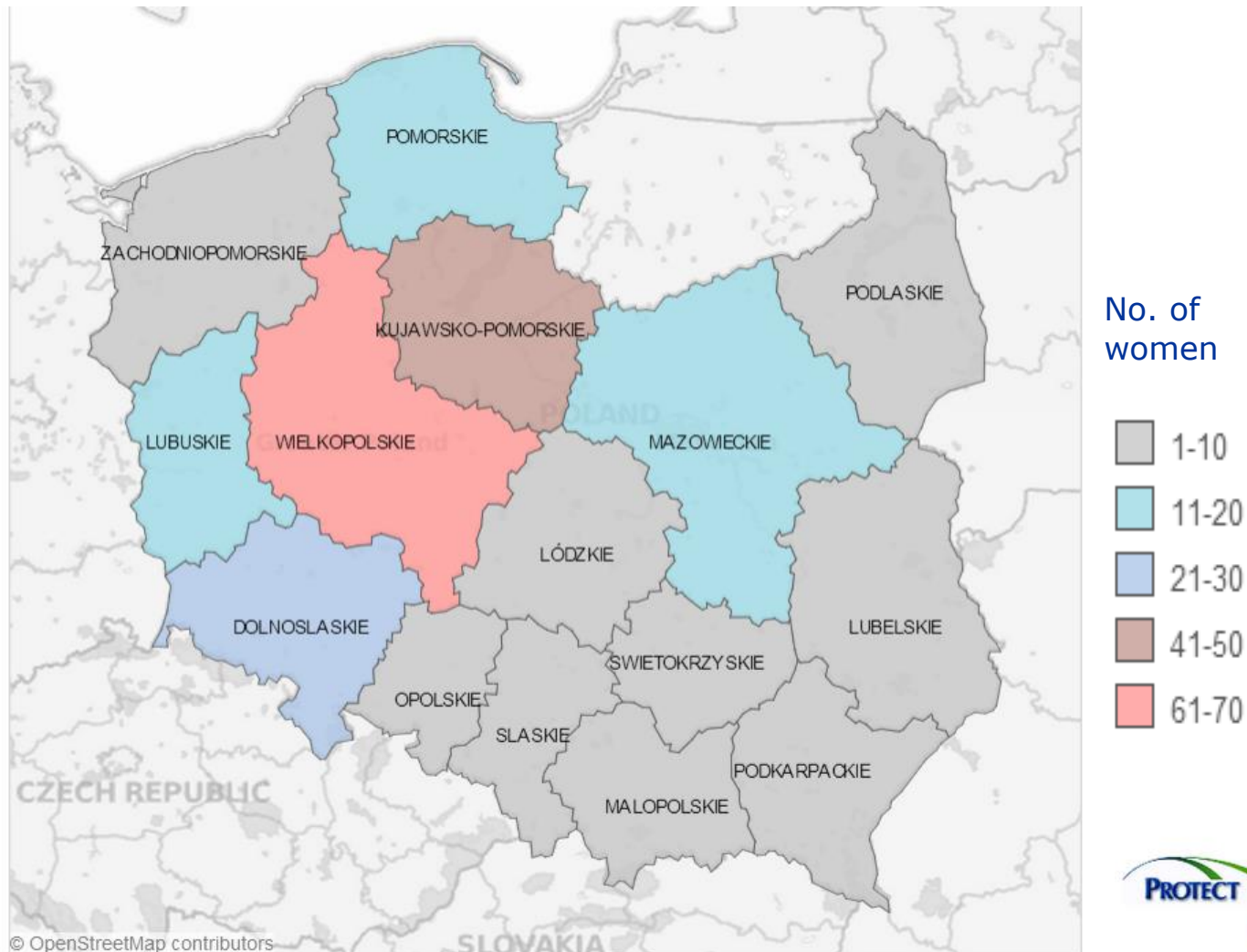


## The Netherlands



No. of  
women

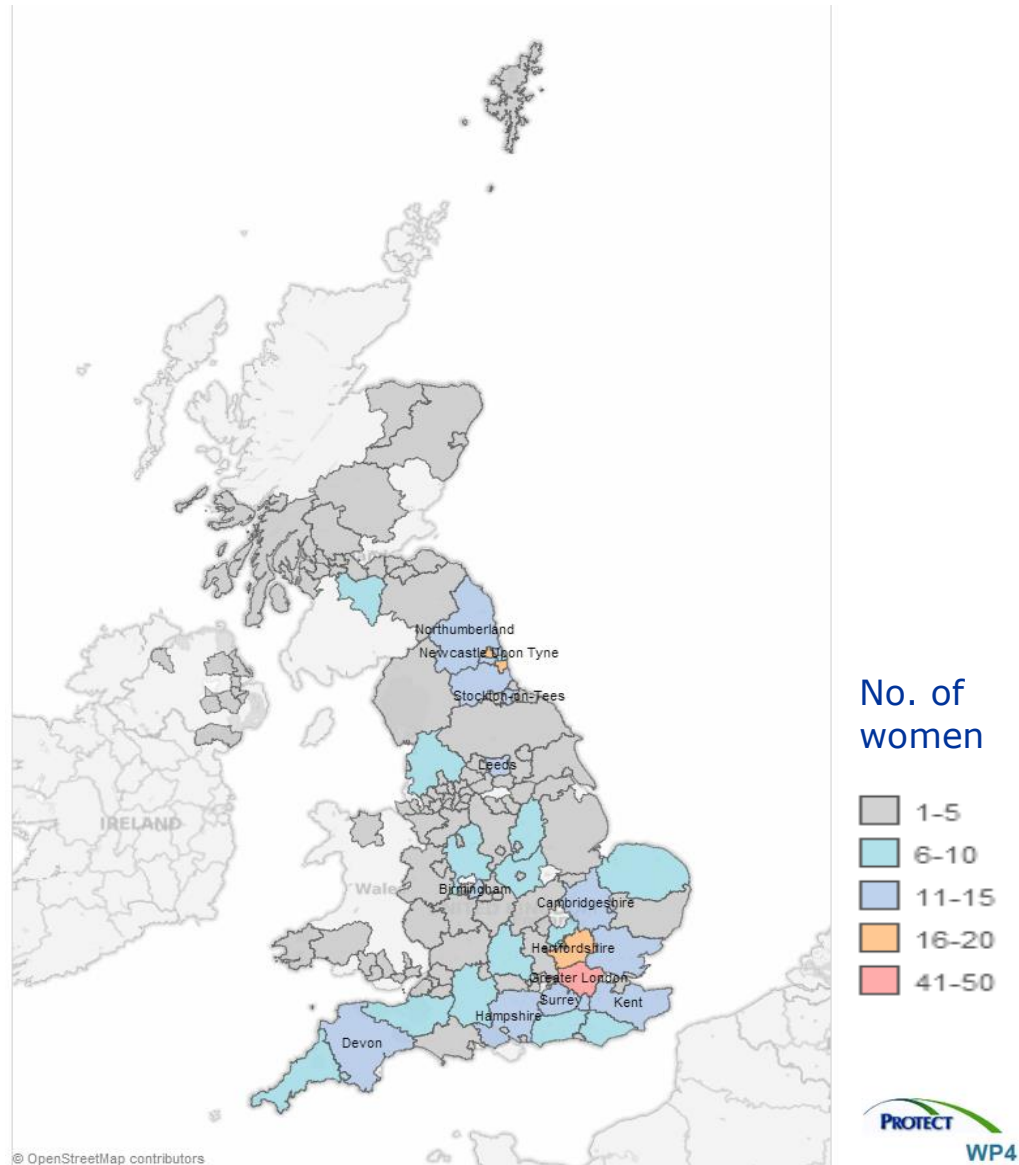




No. of women



## The UK



## Age comparison

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	<b>Denmark PROTECT</b>	<b>Denmark National</b>	<b>UK PROTECT</b>	<b>England &amp; Wales 2013</b>
Age at end of pregnancy, mean (SD)	31.5 (4.6)	30.9 (5.1)	31.7(5.1)	30.0 (NA)
	% (No.)			
<20 years	0.2 (1)*	1.4 (750)	0.7 (5)*	4.2 (29,136)
20-24 years	6.7 (43)	11.2 (6,192)	9.4 (67)	17.1 (119,719)
25-29 years	33.5 (214)	31.0 (17,112)	25.8 (183)	28.2 (196,693)
30-34 years	37.1 (237)	35.0 (19,319)	37.5 (266)	30.4 (212,306)
35-39 years	18.5 (118)	17.7 (9,769)	22.4 (159)	16.0 (111,500)
≥40 years	4.1 (26)	3.8 (2,083)	4.1 (29)	4.2 (29,158)

\* PROTECT lower age restriction for legal reasons



## Age comparison

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	<b>Poland PROTECT</b>	<b>Poland National</b>
Age at end of pregnancy, mean (SD)	29.8 (4.2)	29.2 (NA)
	% (No.)	
<20 years	0.4 (1)*	3.9 (14,552)
20-24 years	12.0 (29)	17.0 (63,158)
25-29 years	45.2 (109)	35.4 (131,373)
30-34 years	32.0 (77)	29.7 (110,192)
35-39 years	9.1 (22)	11.7 (43,554)
≥40 years	1.2 (3)	2.2 (8,133)

\* PROTECT lower age restriction for legal reasons

## Education comparison

	<b>Denmark PROTECT</b>	<b>Denmark National</b>	<b>UK PROTECT</b>	<b>UK 2011 (m + f)*</b>
Completed legal part of school and 1 <sup>st</sup> level of exams	2.8%	15.3%	12.6%	44.4%
Completed school and the higher level exams	11.7%	32.8%	21.7%	21.8%
Completed some kind of 3 <sup>rd</sup> level education- university, technical college etc	46.7%	30.9%	35.6%	33.0%
Completed university and some post-grad education	38.8%	14.6%	30.2%	NA
Not stated	0.8%	6.3%	0.4%	0.8%

## Education comparison

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	<b>Poland PROTECT</b>	<b>Poland National</b>
Completed legal part of school and 1 <sup>st</sup> level of exams	1.7%	7.0%
Completed school and the higher level exams	8.8%	55.7%
Completed some kind of 3 <sup>rd</sup> level education- university, technical college etc	23.4%	0.6%
Completed university and some post-grad education	66.1%	32.6%
Not stated	0.8%	0%

What can be learned from asking “patients” directly and how much of that is not available elsewhere?



## Number of different medicinal products taken during pregnancy\*

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No. of Medicinal Products Taken	DK % (n)	NL % (n)	PL % (n)	UK % (n)	Total % (n)
None	18% (117)	21% (98)	24% (59)	13% (90)	<b>18% (364)</b>
1	16% (102)	23% (109)	22% (54)	17% (119)	<b>19% (384)</b>
2	17% (108)	17% (81)	15% (37)	16% (113)	<b>16% (339)</b>
3	14% (90)	16% (74)	12% (28)	15% (108)	<b>15% (300)</b>
4	11% (73)	8% (37)	8% (19)	10% (74)	<b>10% (203)</b>
≥ 5	23% (149)	16% (77)	18% (44)	29% (205)	<b>23% (475)</b>

\* Excluding iron, folate and multi-vitamins

## Vaccinations during or month before

	<b>DK (%)</b>	<b>NL (%)</b>	<b>PL (%)</b>	<b>UK (%)</b>
Vaccination	14.4	4.0	2.5	48.7
Flu	6.4	2.7	0.8	46.1
Measles	0.0	0.2	0.0	0.6
Mumps	0.0	0.2	0.0	0.6
Rubella	0.0	0.2	0.0	0.6
BCG (TB)	0.0	0.0	0.0	0.3
Hep A	0.2	0.4	0.0	0.3
Hep B	0.2	0.2	0.4	0.1
Typhoid	0.2	0.4	0.0	0.1
HPV	5.9	0.0	0.0	0.1

## Life style factors

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	DK (%)	NL (%)	PL (%)	UK (%)
Pregnant while using contraception	3.3	3.2	2.5	6.1
Took “morning after pill”	0.3	2.1	0.8	1.3
Smoker before pregnancy	16.6	14.3	18.7	16.1
Smoker during pregnancy	4.1	4.2	4.6	4.8
Alcohol				
2-3 times / week	0.3	0.2	0.0	0.6
2-4 times/month	6.1	0.6	0.0	10.7
≤ 1 per month	20.7	6.1	11.6	21.4
Never	72.6	92.6	87.6	66.6
Unknown	0.3	0.4	0.8	0.6
<i>Recreational drug use</i>	<i>0.9</i>	<i>0.4</i>	<i>0.4</i>	<i>1.1</i>
<i>Undisclosed recreational drug use</i>	<i>0.6</i>	<i>0.2</i>	<i>2.9</i>	<i>0.4</i>

## Other medication use & risk factors

	<b>DK (%)</b>	<b>NL (%)</b>	<b>PL (%)</b>	<b>UK (%)</b>
Decided not to take a prescribed medicine	4.9	4.0	4.6	5.5
Took prescribed medicine from friend or family	0.3	0.6	0.4	0.7
Anaesthetics	4.9	8.8	11.6	7.1
General	0.6	1.1	0.4	0.6
Spinal	0	0	0	0.3
Local	4.1	7.6	10.0	5.9
Did not know type	0.2	0.2	1.2	0.3
X rays	6.9	4.6	3.7	4.9
Herbal medicines	4.3	7.8	0	6.6
OTC medications*	68.5	65.1	47.3	76.4

\* Includes those available through both prescription and OTC



## Outcomes of pregnancy

	<b>DK N=177</b>	<b>NL N=92</b>	<b>PL N=35</b>	<b>UK N=157</b>	<b>Total</b>
<b>Live birth</b>	83% (147)	96% (88)	92% (35)	96% (151)	91% (421)
<b>&lt;20w foetal death</b>	14% (24)	0% (0)	5% (2)	3% (4)	6% (30)
<b>≥20w foetal death</b>	2% (4)	0% (0)	3% (1)	0% (0)	1% (5)
<b>Termination</b>	0.6% (1)	2% (2)	0% (0)	0% (0)	1% (3)
<b>Ectopic pregnancy</b>	1% (1)	0% (0)	0% (0)	0% (0)	0% (1)
<b>Unknown</b>	0% (0)	2% (2)	0% (0)	1% (2)	1% (4)

## “Visible Birth Defects” among live births

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Country Number of live births	DK N=148	NL N=90	PL N=36	UK N=155	Total N=429
Reported a visible birth defect	2.0% (3)	0.0% (0)	2.8% (1)	3.2% (5)	2.1% (9)
Ankyloglossia				2	0.5% (2)
Absence of hand or finger			1		0.2% (1)
Malformation of face & neck	1				0.2% (1)
Malformation of heart, unspec				1	0.2% (1)
Down Syndrome				1	0.2% (1)
Hypospadias, balanic	1				0.2% (1)
Malformation of tongue, unspec	1				0.2% (1)
Pilar & trichodermal cyst				1	0.2% (1)
<i>Not sure / No response</i>	3.4% (5)	6.7% (6)	0	1.3% (2)	3.0% (13)

# Are self-reported data reasonably accurate?

- Medication use
- Other risk factors
- Outcomes



## Comparing self-reported medication use with Danish Prescription Register

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**selected examples from 637 Danes**

Drugs for Chronic Conditions	Reported in both* (PROTECT/ Register)	Reported only in PROTECT†
<i>All Drugs for Chronic Conditions</i>	<i>80% (174/217)</i>	
Oral anti-diabetics	100% (5/5)	1
Opioids	88% (7/8)	6
Anti-depressants	94% (29/31)	5
Anti-asthmatics	83% (29/35)	17

\* Includes medications reported as prescribed but not taken

† Not found in register up to 6 months prior to conception date

# Comparing self-reported medication use with Danish Prescription Register

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## selected examples

Drugs for Occasional or short-Term Use	Reported in both* (PROTECT/ Register)	Reported only in PROTECT†
<i>All Drugs for Occasional or Short-Term Use</i>	<i>54% (154/285)</i>	<i>59</i>
Corticosteroids, dermatologic use	30% (6/20)	4
Antibiotics, systemic	64% (112/174)	12
Anxiolytics, hypnotics and sedatives	0% (0/1)	3

\* Includes medications reported as prescribed but not taken

† Not found in register up to 6 months prior conception date

# Comparing self-reported medication use with Danish Prescription Register

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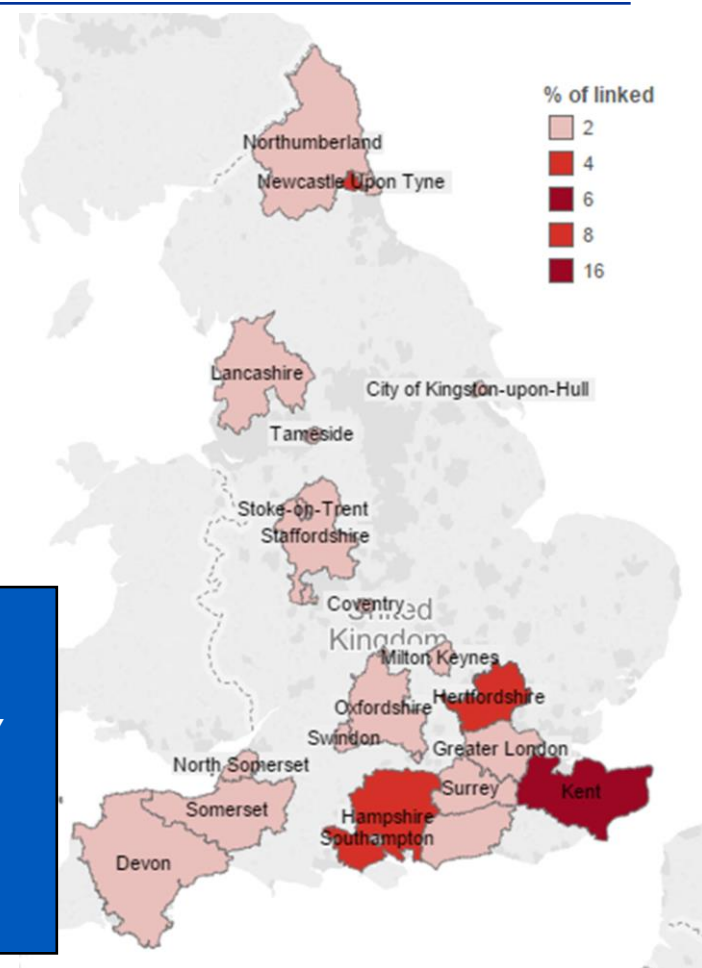
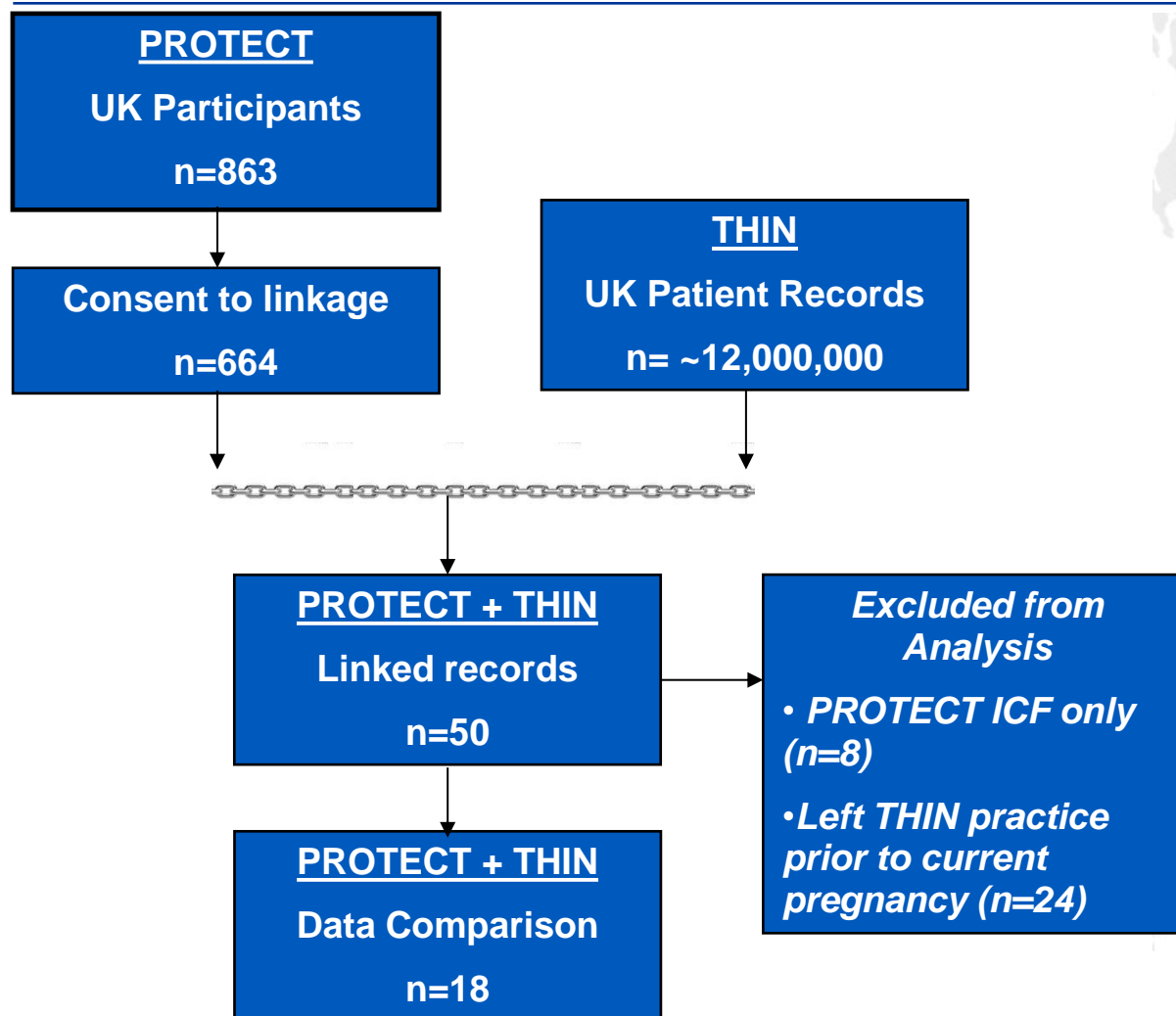
## selected examples

Pregnancy-Related Medications	Reported in both* (PROTECT/ Register)	Reported only in PROTECT†
<i>All Pregnancy-related medications</i>	56% (66/118)	35
Anti-emetics	60% (9/15)	2
Hemorrhoids treatment	48% (11/23)	3
Progesterone	80% (20/25)	3

\* Includes medications reported as prescribed by not taken

† Not found in register up to 6 months prior conception date

# UK PROTECT-THIN linkage



## Comparing self-reported medication use with THIN database

	Reported in both* (PROTECT/ THIN)	Reported only in PROTECT†
Drugs for chronic conditions	3/6 (50%)	4
Drugs for occasional or short term use	4/12 (33%)	1
Pregnancy related medications	6/10 (60%)	2

\* Includes medications reported as prescribed but not taken

† Not found in THIN up to 6 months prior to conception date or during pregnancy



## Comparing pregnancy outcome information in THIN

	Reported in PROTECT	Not reported in PROTECT	
Reported in THIN	2 (13%)	10 (63%)	12 (75%)
Not reported in THIN	3 (19%)	1 (6%)	4 (25%)
	5 (31%)	11 (69%)	16 (100%)

Are these data reliable enough for  
Pharmacovigilance purpose?



## **Patient-Reported Medication Use - strengths**

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- Can recruit women in early stages of pregnancy but careful choice of recruitment methods required
- Women likely to report medications in drug categories which include medications purchased over-the-counter (OTC) (e.g. analgesics, drugs for acid related disorders etc.)
- Can provide useful information on prn medicines prescribed a long time before the pregnancy and “borrowed” medicines

## Other Strengths

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- May provide more accurate data on adherence since respondents will report prescriptions not filled or not taken.
- Respondents will report about illicit and recreational drug use, and shared medications
- Good for medications taken to treat short-term illnesses

## Limitations

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- Like every prospective study, direct-to-consumer studies will benefit from substantial attention (and funding) for recruitment and retention.
- Incomplete reporting of prescription medicinal products but also reports of prescription drugs not found in the register
- Unknown validity of reports on OTC and herbals
- May be difficult to obtain complete and accurate reporting about pregnancy outcomes.

## Conclusion

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- It is possible to recruit women early in pregnancy before they may have consulted HCPs
- Direct to consumer studies offer important benefits in collecting certain data not found in EHR
- Will be most informative when combined with selected data from other sources to validate clinical outcomes of interest, and to corroborate most important exposures

## **Q&A**

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