Data-driven transgender health care

reconnecting personalized care and clinical research

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Amsterdam UMC

EPATH
11-13 AUGUST 2021
GOTHENBURG, SWEDEN

Health care and science: friends or rivals

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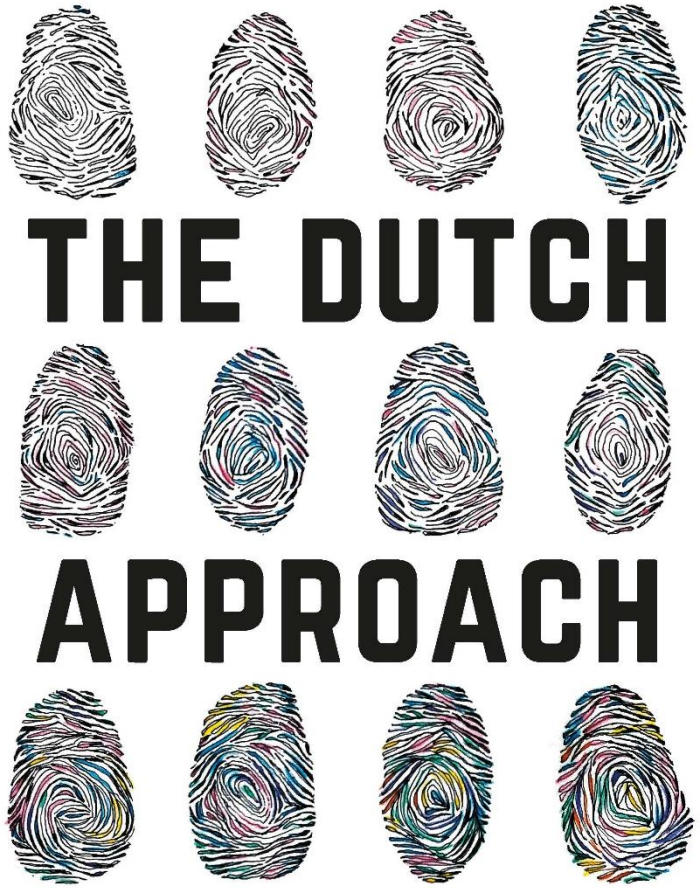
DATA

ALEX BAKKER



THE DUTCH APPROACH

FIFTY YEARS OF TRANSGENDER HEALTH CARE AT THE VU AMSTERDAM GENDER CLINIC

Boom

© MARC DRIESSEN

ALEX BAKKER (1968) is a Dutch historian and writer, specializing in transgender history. In 2018 he published *Transgender in the Netherlands: an extraordinary history*, the first overview on this topic. Bakker also works as a researcher and writer for exhibitions and documentary films. In 2014 he published his autobiographical book *My untrue past*.

WWW.BOOMGESCHIEDENIS.NL
WWW.BOOMUITGEVERSAMSTERDAM.NL

9 789024 444687 >

“There was hardly any expertise on cross-sex hormones, certainly not based on systematically collected data.

So, I looked at existing medical knowledge of non-transgender people with variant sexual differentations.”

“I was well aware of the risks of long-term side effects.

We knew that a high dose of sex hormones impacts the cardiovascular system and the development of tumors. So, it was looking for balance. In medicine, there just are certain risks and side effects you have to take for granted.

Nevertheless, that fear was always in the back of my mind. With other problems, like diabetes, there are thousands of colleagues all over the world you can consult. We didn’t have that.

Nowhere in the world, systematic scientific research into the effects of sex reassignment treatment was done. That’s why I felt it was extremely important to do as much research as possible and discover the side effects myself.

Keep my own house clean, so to speak.”

Current practice

- Combined PhD and working as doctor in the clinic
- Informed consent to reuse clinical data for research
- Questionnaires
- ‘Loosely’ standardized treatment protocol
- Simple research questions, mostly originating from the consulting room!

ENIGI

The Journal of Sexual Medicine

Volume 13, Issue 6, June 2016, Pages 994–999

Original Research

A European Network for the Investigation of Gender Incongruence: Endocrine Part

M.J.H.J. Dekker, MD, PhD[1], K. Wierckx, MD, PhD[2], E. Van Caenegem, MD, PhD[2], M. Klaver, MD[1], B.P. Kreukels, PhD[3], E. Elaut, PhD[4], A.D. Fisher, MD, PhD[5], M.A.A. van Trotsenburg, MD[6], T. Schreiner, MD[7], M. den Heijer, MD, PhD[1], G. T'Sjoen, MD, PhD[2, 4]

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[7] Department of Endocrinology, Oslo University Hospital, Oslo, Norway

Received 2 November 2015, Accepted 28 March 2016, Available online 6 May 2016

	Pretreatment phase	Treatment phase												
Visit no.	1	2	3	4	5	6	7	8	9	10				
Study week	-6 to 0	6-12	24	36	48	72	96	120	144	…	Yearly after SRS			
Study month	0	1 ½ - 3	6	9	12	18	24	30	36	…				
Blood chemistry[3]	x	x	x		x	x	x	x	x	x	x	x	x	x
Hormonal parameters[4]	x	x	x		x	x	x	x	x	x	x	x	x	x
Genetic samples	x													
Serum bank	x				x		x	To be discussed						
OGTT/Matsuda index[5]	x				x		x							
Bone mineral density/ body composition (whole body, lumbar spine, hip)[6]	x				x		x							5
Baecke questionnaire	x				x		x							x
Klimax score	x	x	x		x		x		x					
VHI[7]	x	x	x		x		x		x					
Adverse events	as required+													

Topics in ENIGI

• Body composition	Klaver et al, EJE 2018
• Bone density	Wiepjes et al, JBMR 2017
• Lipids	Van Velzen, JCEM 2019
• Breast development	de Blok et al, JCEM 2018
• Facial features	Tebbens et al , JSM 2019
• Subjective effects	van Dijk et al, JSM 2019
• Hematocrit	Defreyne, Andrology, 2018
• Bone markers	Vlot et al, JBMR, 2019
• Vaginal bleeding	Defreyne, IJTH, 2020
• Sexual desire	Defreyne, IJTH, 2020
• Coagulation	Scheres et al, JTH 2021
• Liver enzymes	Stangl et al , EJE 2021
• CVD risk	Cocchetti et al, JSM 2021

Short-term effects hormone therapy

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

[a]Prevention and treatment as recommended for biological men.

[b]Menorrhagia requires diagnosis and treatment by a gynecologist.

Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

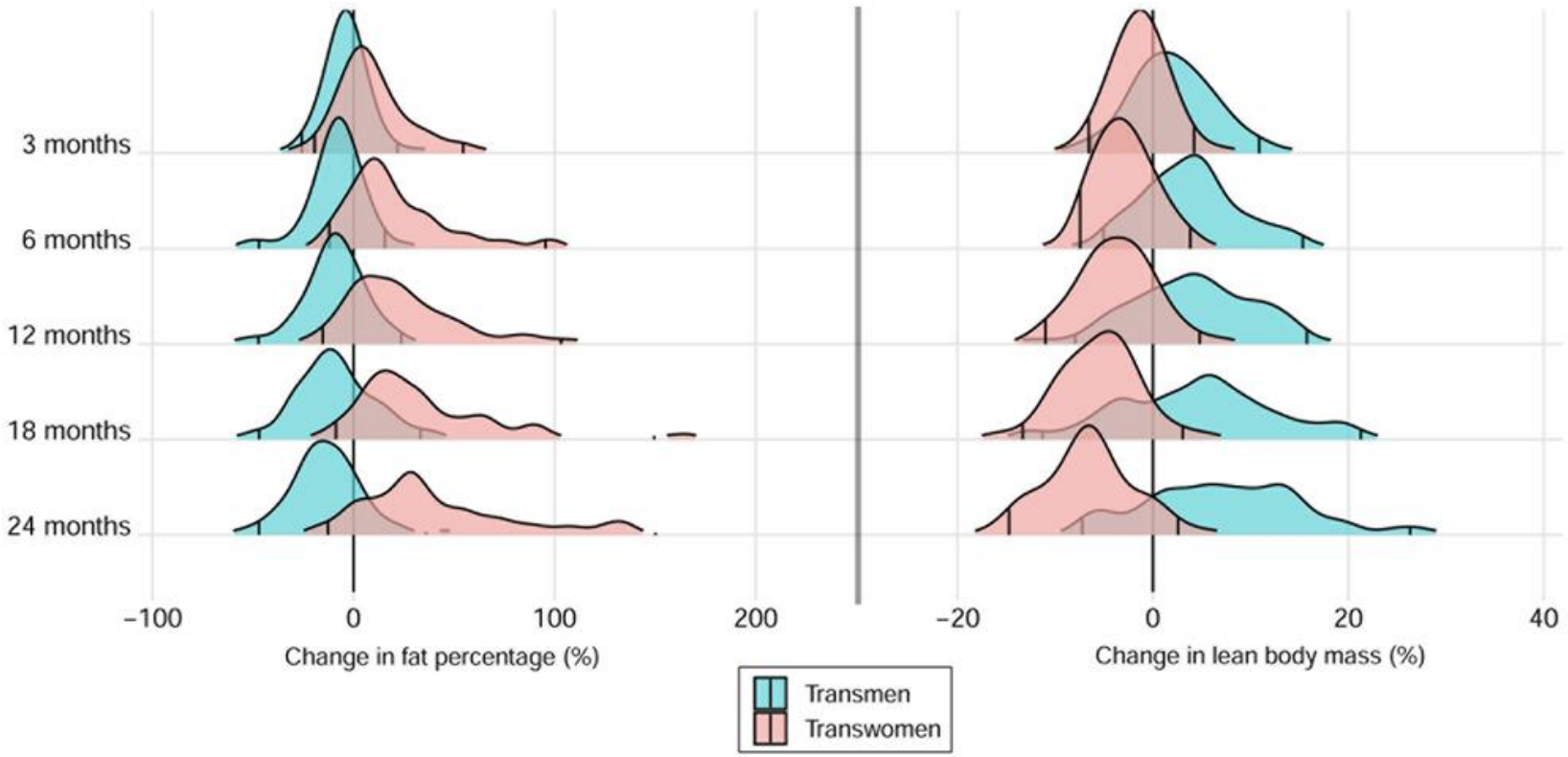
[a]Complete removal of male sexual hair requires electrolysis or laser treatment or both.

[b]Familial scalp hair loss may occur if estrogens are stopped.

[c]Treatment by speech pathologists for voice training is most effective.

JCEM, 2017

Mean effect vs distribution of effects



van Velzen et al, EJE 2020

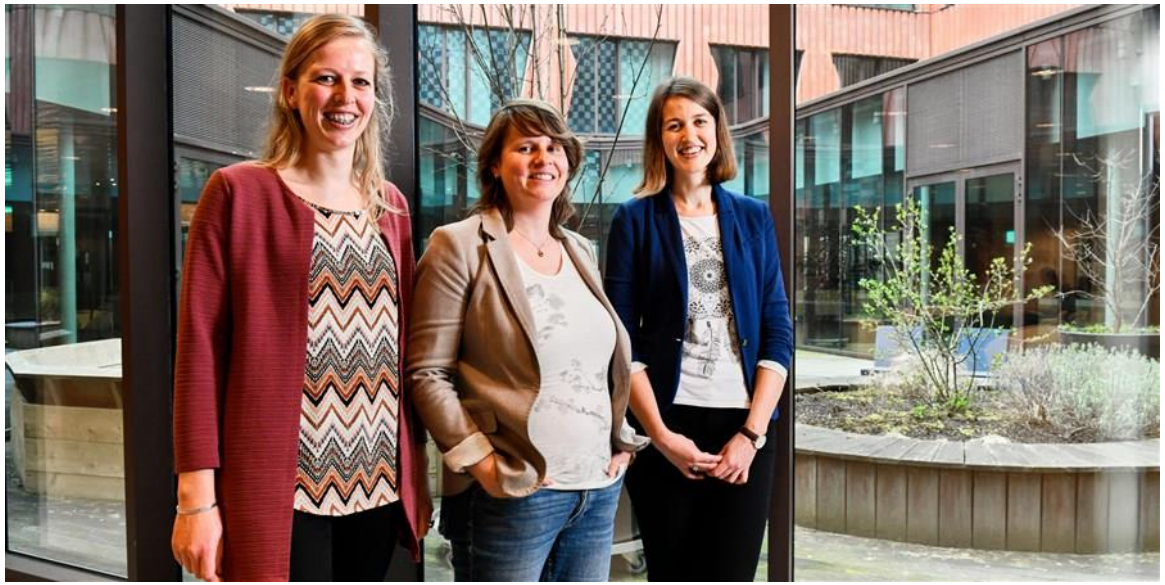
Amsterdam Cohort of Gender Dysphoria (ACOG)

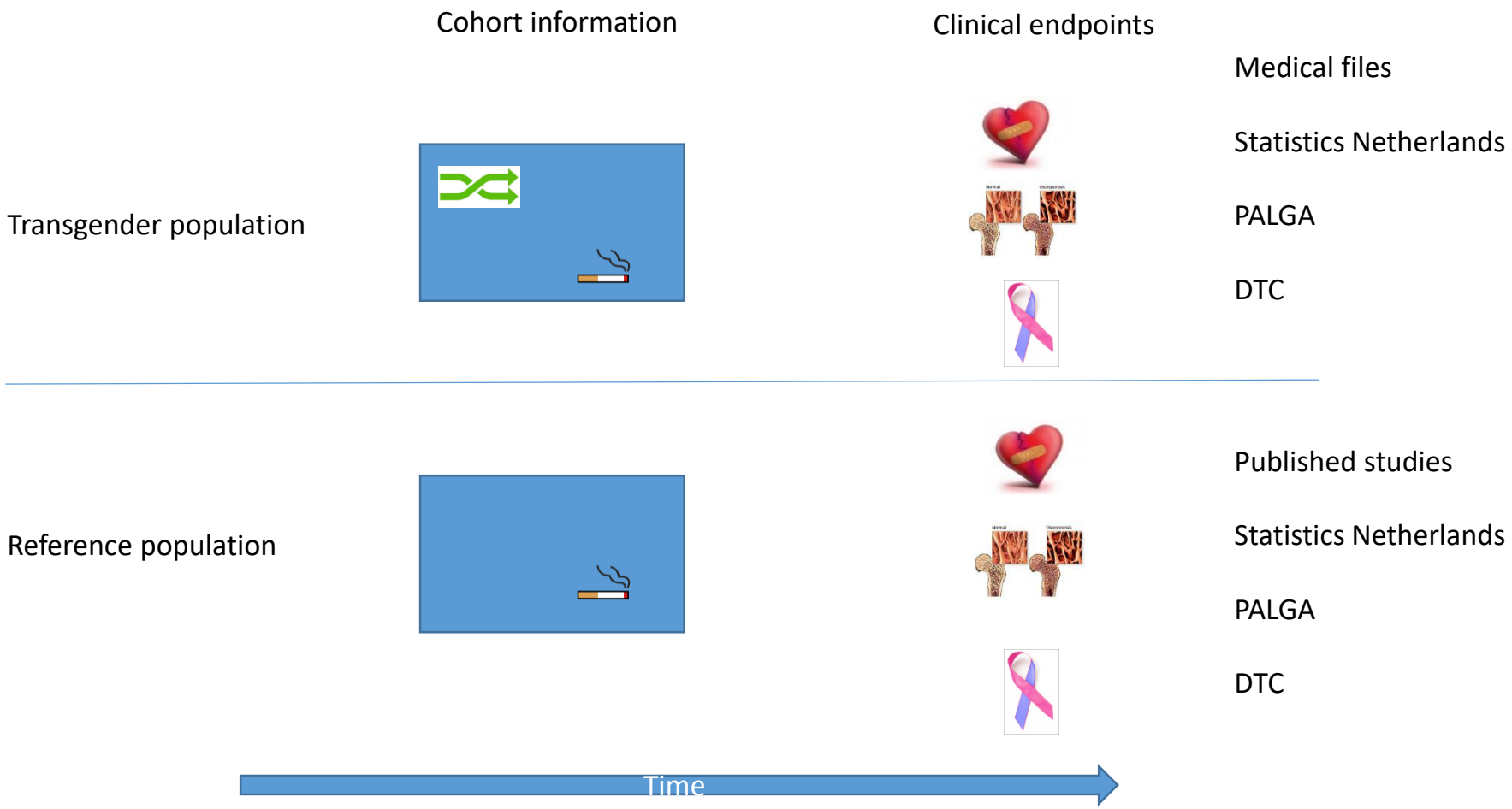
Wiepjes et al. J Sex Med (2018)

	Trans women	Trans men
Total number people	4,432	2,361
Adults ≥18 years	3,809	1,624
Age, yr (median, IQR, max)	33 (25 – 42; 81)	25 (21 – 35; 73)
start HT	69%	73%
gonadectomy	75%	84%

Linking to registries

Statistics Netherlands

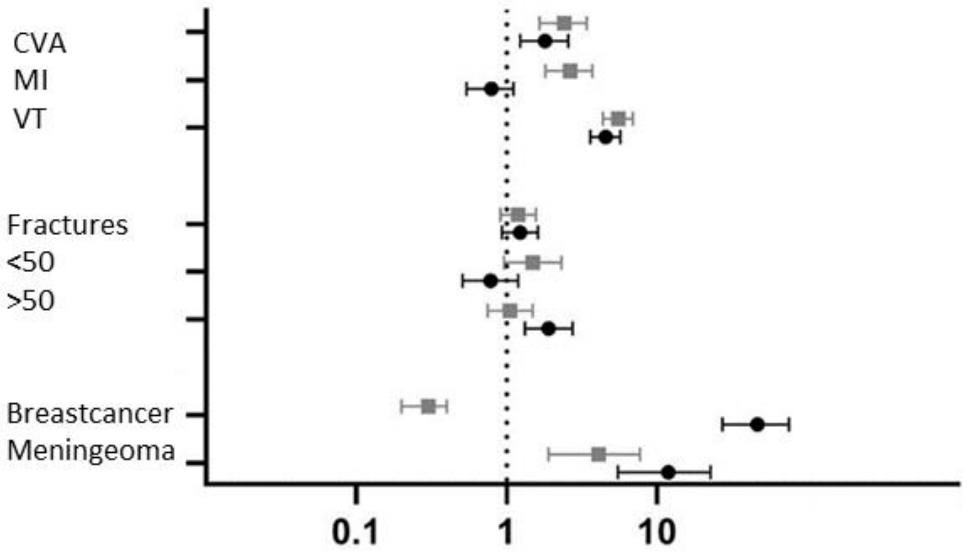


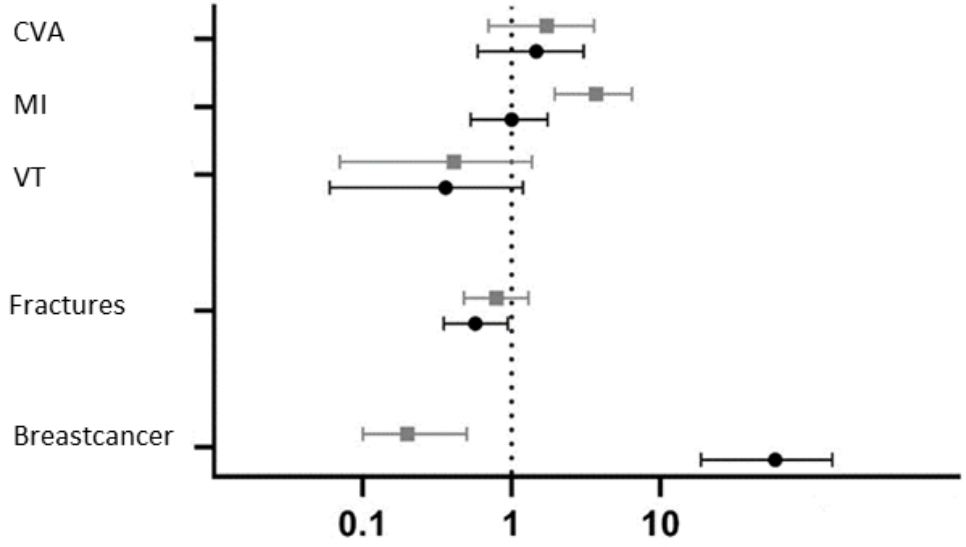

Cohort information
Clinical endpoints
Medical files
Statistics Netherlands
PALGA
DTC
Transgender population
Reference population
Published studies
Statistics Netherlands
PALGA
DTC
Time

Topics ACOG

• Meningeoma	Nota et al, Brain 2018
• CVD/Thrombosis	Nota et al, Circulation 2019
• Breast cancer	de Blok et al, BMJ 2019
• Bone density	Wiepjes et al, JBMR 2019
• Fractures	Wiepjes et al, JBMR 2019
• Suicide	Wiepjes et al, Acta Psychiatr Scand 2020
• Prostate cancer	de Nie et al, JCEM 2020
• Erythrocytosis	Madsen et al, JCEM 2021
• Cognitive functioning	van Heesewijk, JSM 2021
• Testis cancer	de Nie et al, BJU in press
• Mortality	de Blok et al, Lancet D&E in press

Long-term risks of hormone therapy





- cis men as reference category
- cis women as reference category

de Blok, NTVG 2020

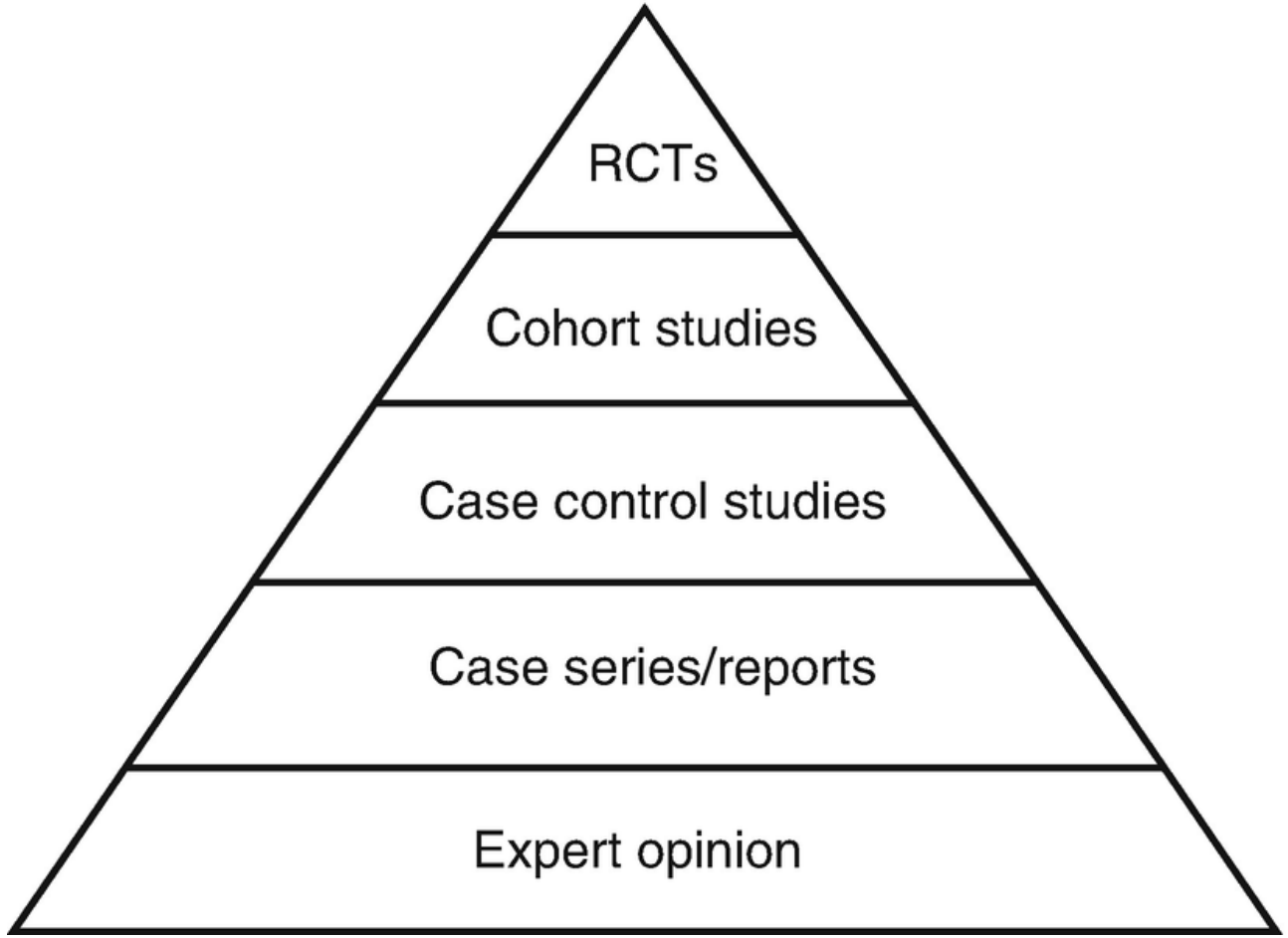
Concrete results for transgender health care

- Stopping of preoperatively cessation of hormones
- Stopping routine bone density measurements
- Cleaning up routine blood tests (~~prolactine, LF~~)
- More aware of side-effects of cyproterone acetate, switch to GnRHa
- Adjustment of target levels of sex hormones
- More awareness for participation in cancer screening programs

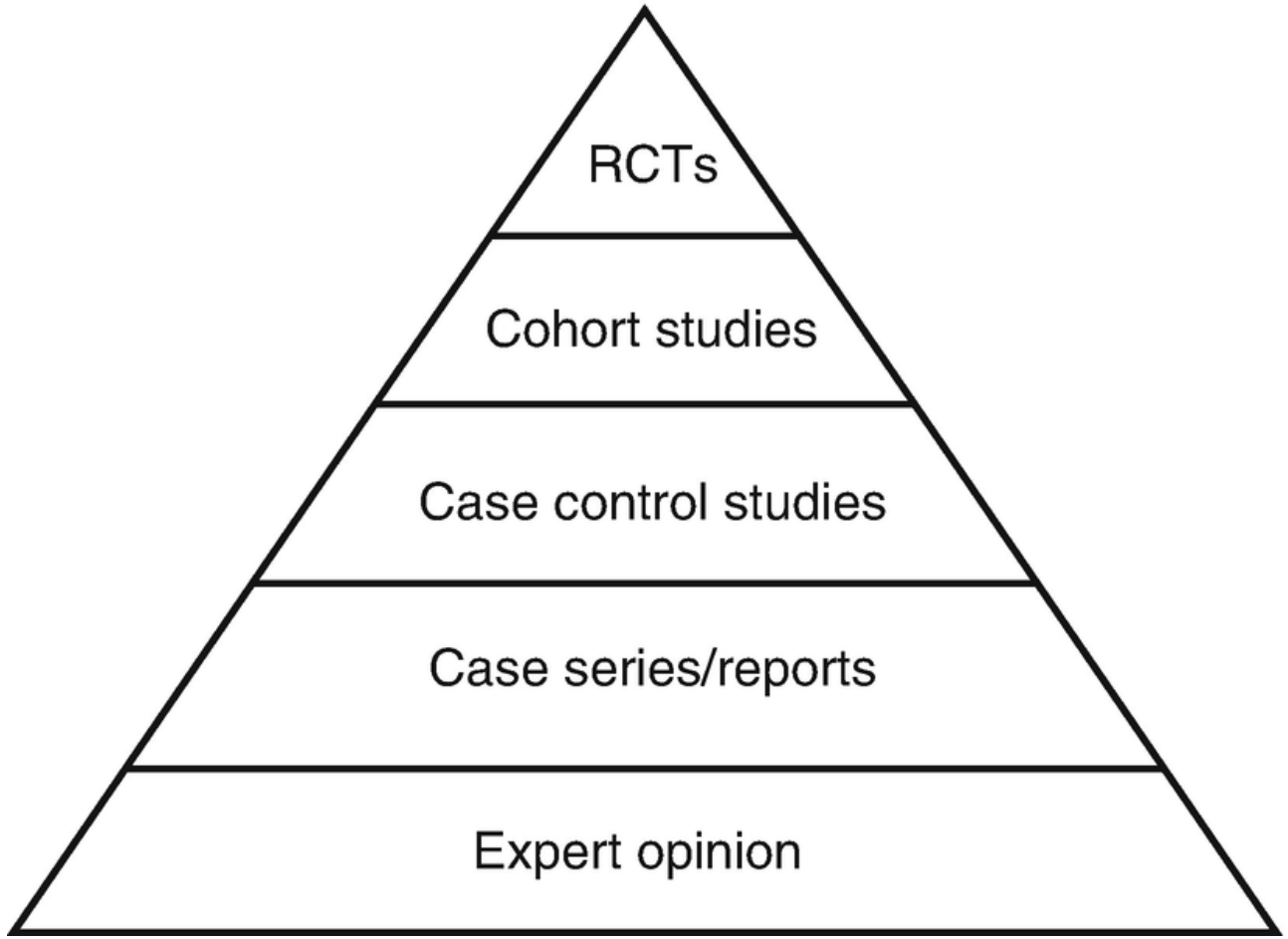
Possible frictions between care and research

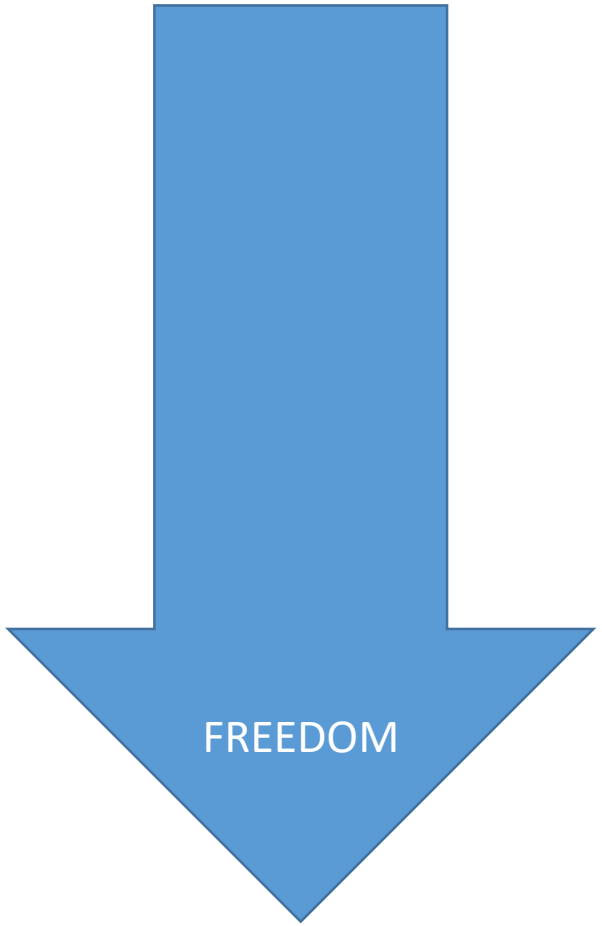
- Ethics of randomization, standardization and uniformation
- Privacy and consent issues

Hierarchies of Evidence

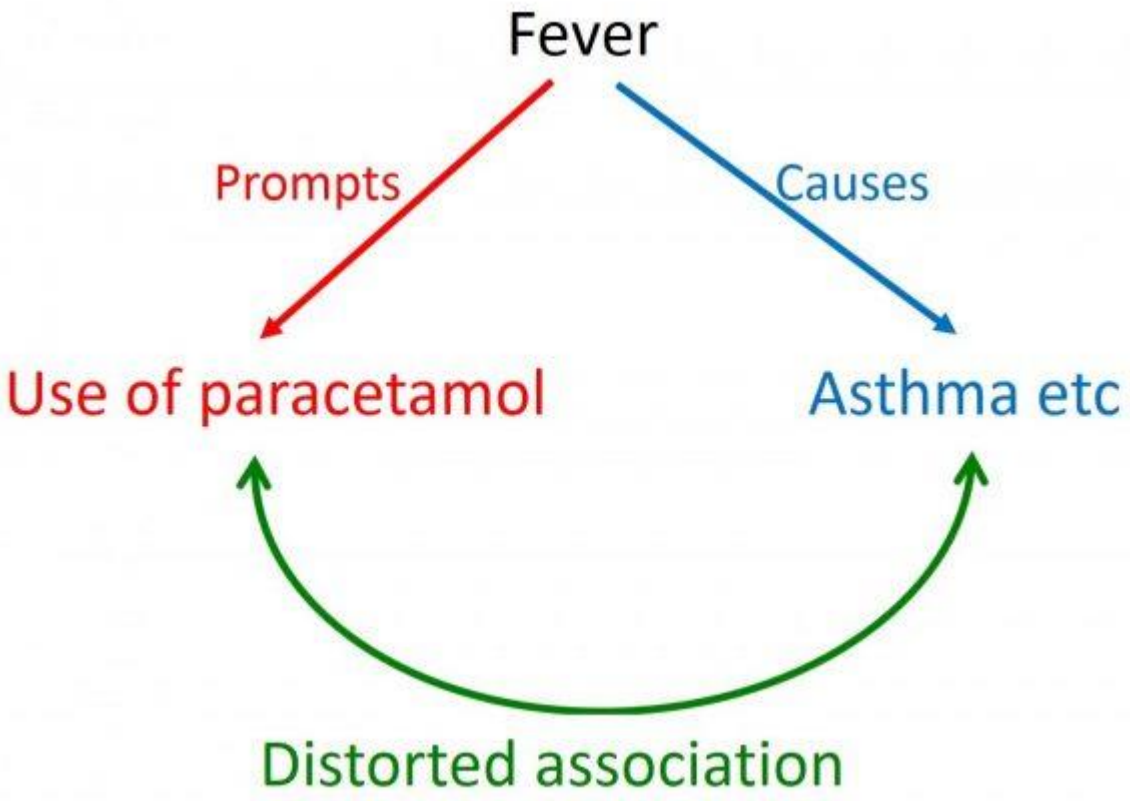


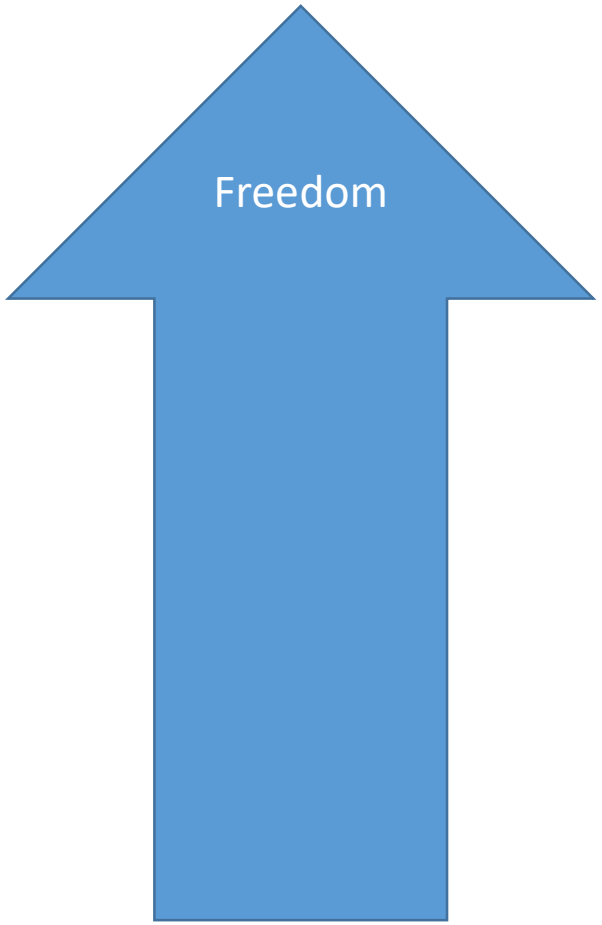
Hierarchies of Evidence





Bias by indication





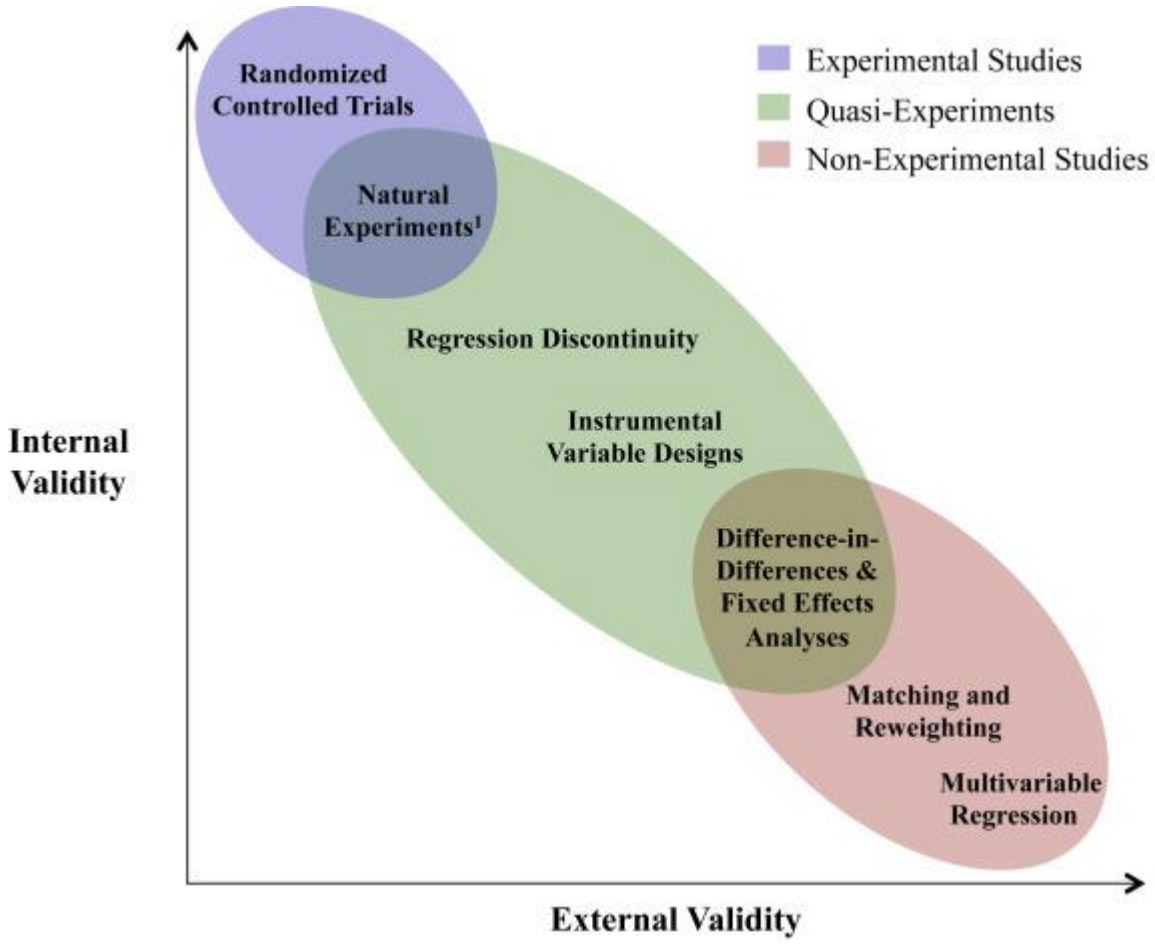
Privacy and consent issues

Possible frictions between care and research

- Ethics of randomization, standardization and uniformation
- Privacy and consent issues

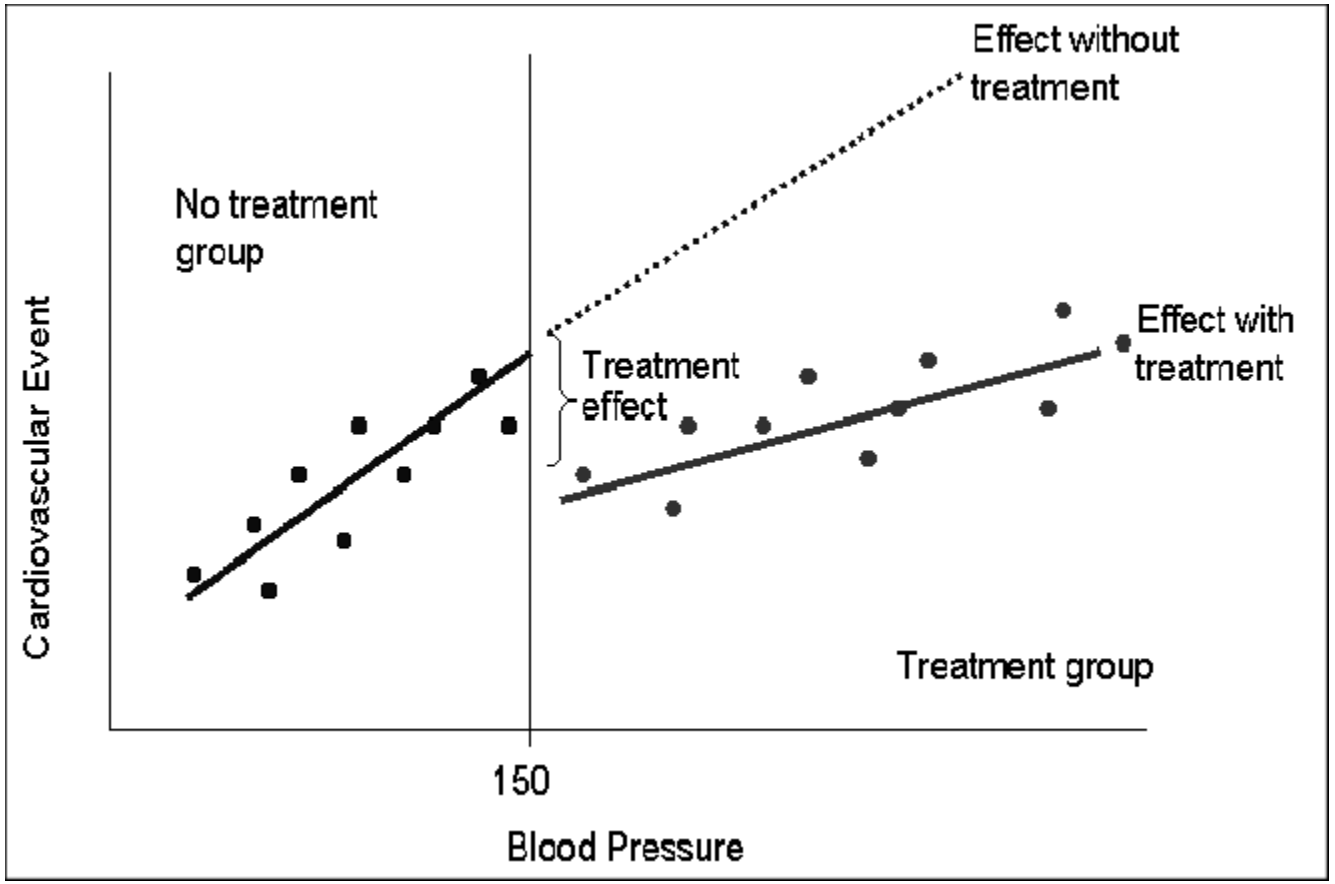
Solutions?

Quasi-Experimental studies



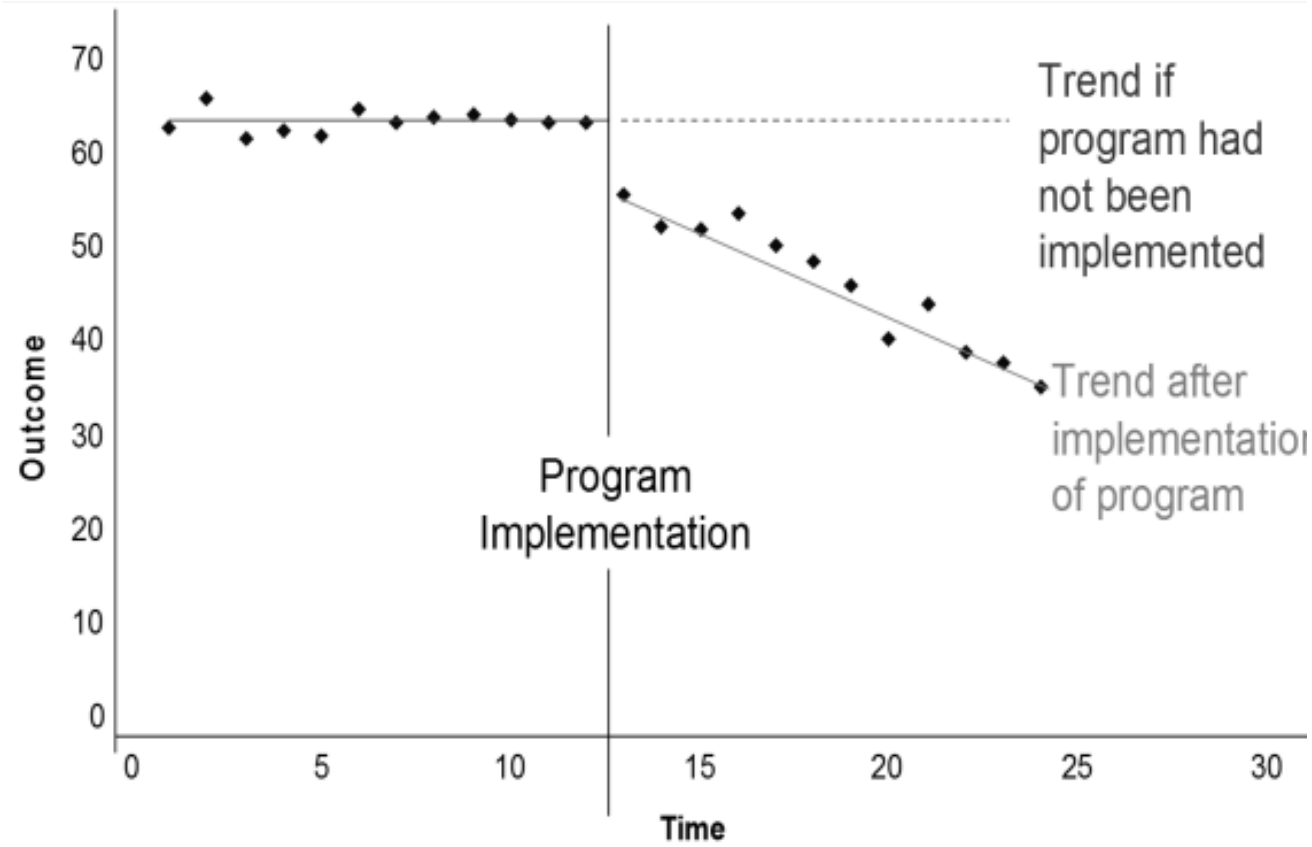
Geldsetzer, Fawzi; JCE, 2017

Regressions Discontinuity Design

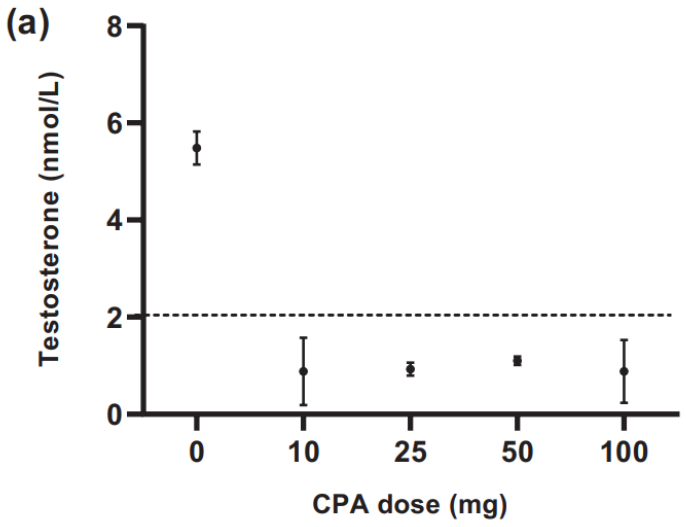


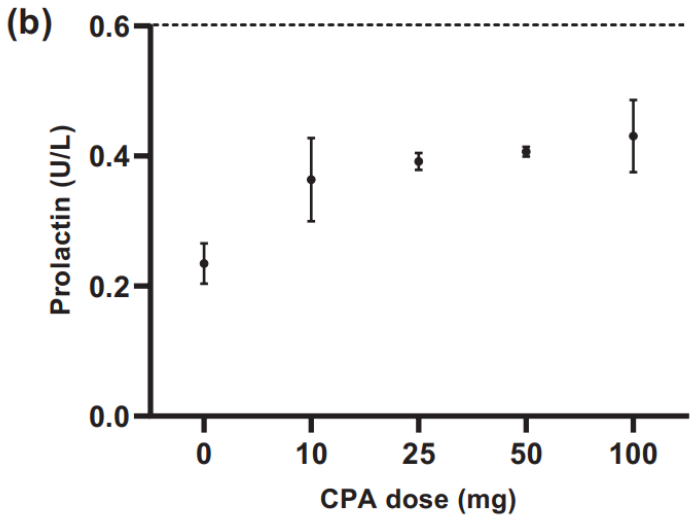
Tsai, et al Asian/Pacific Island Nursing Journal, 2016.

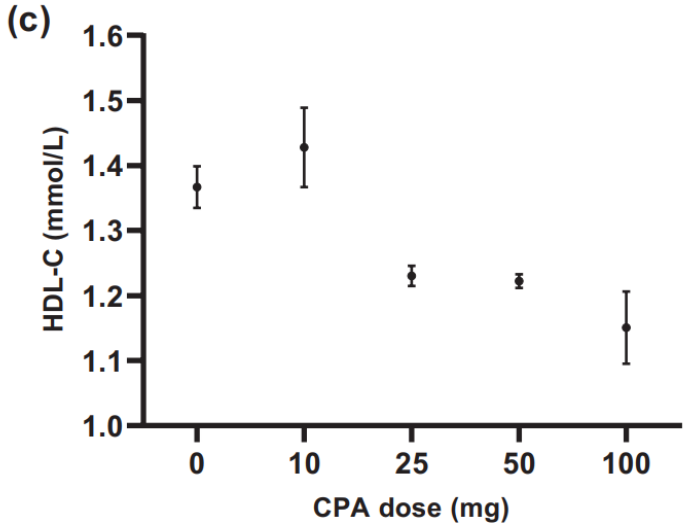
Interrupted Time-series Design



Tsai, et al Asian/Pacific Island Nursing Journal, 2016.

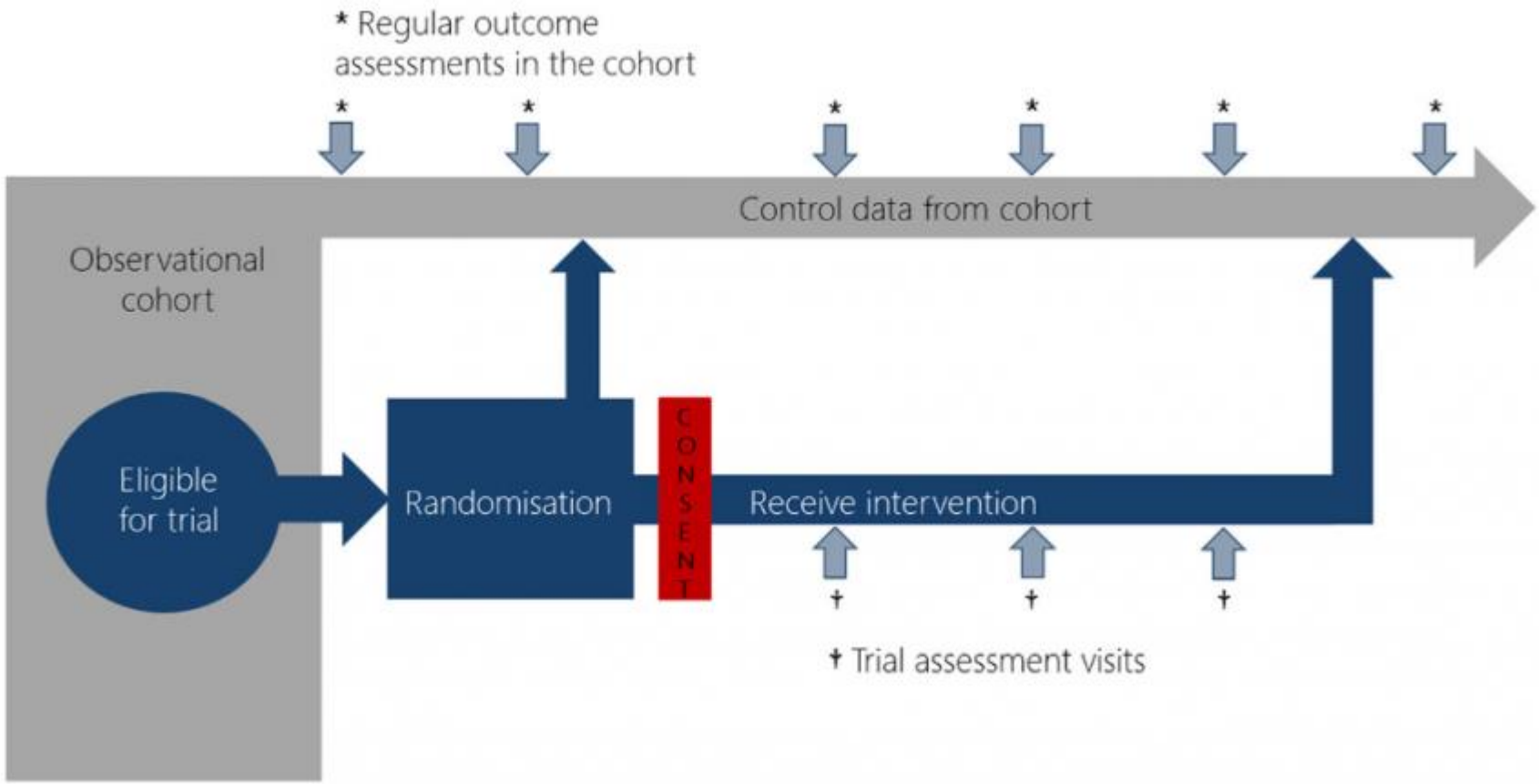






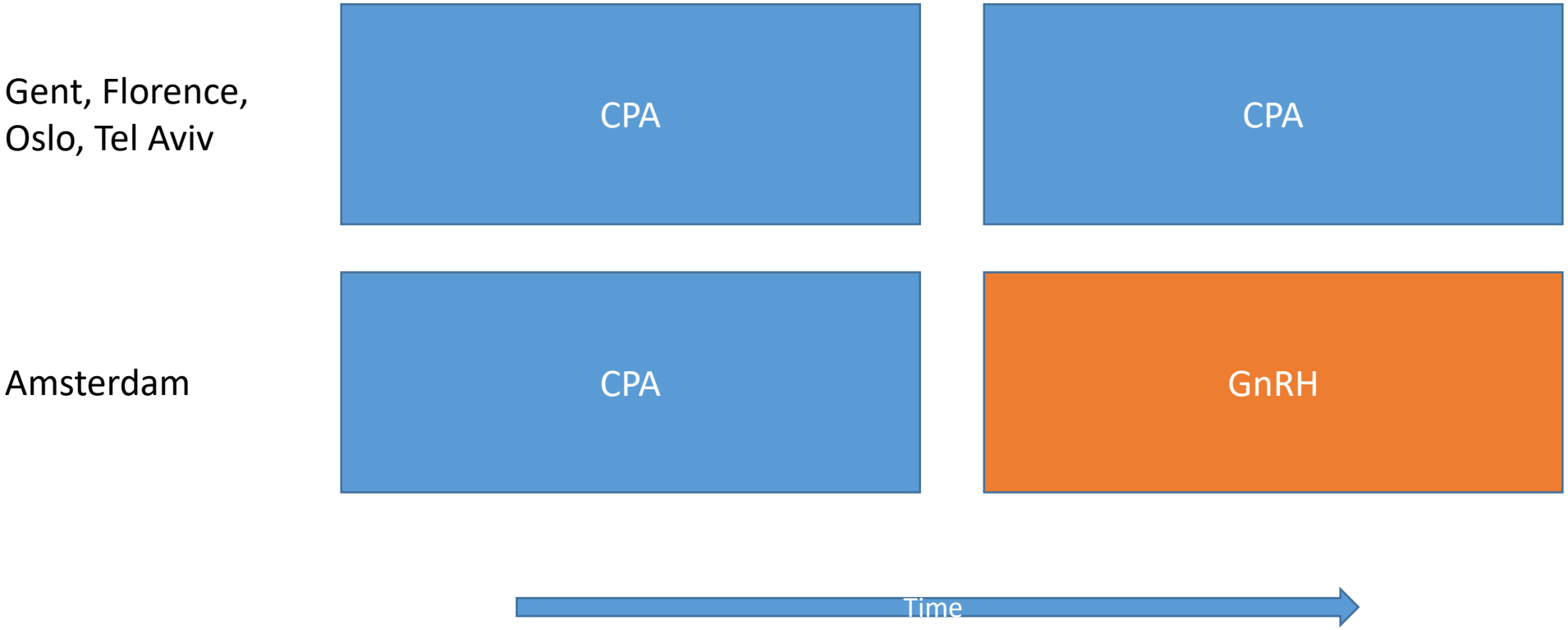
Kuijpers et al, JCEM 2021

Trial within cohort design



trialsjournal.biomedcentral.com

Non-equivalent Control Group Design

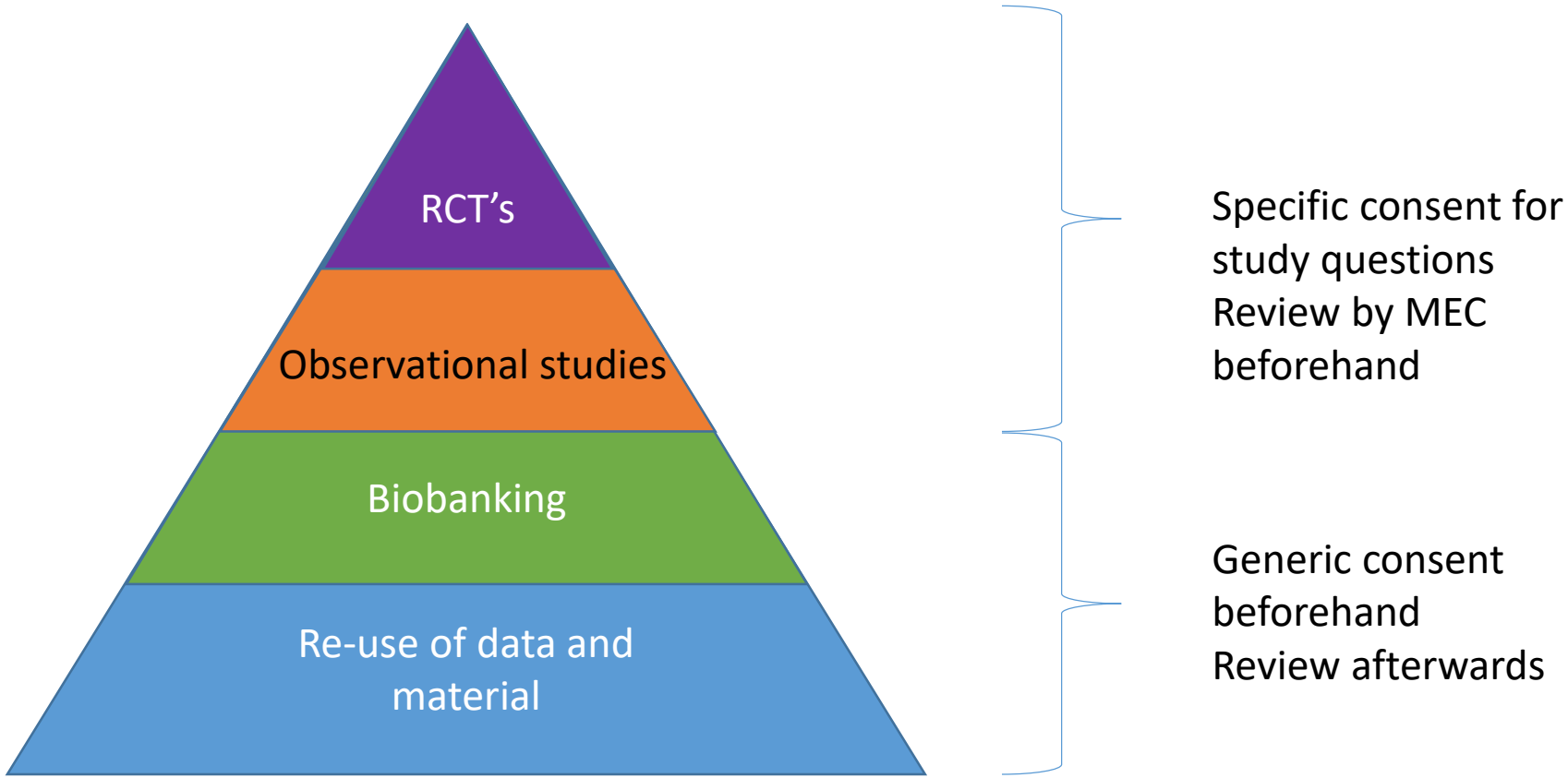


Possible frictions between care and research

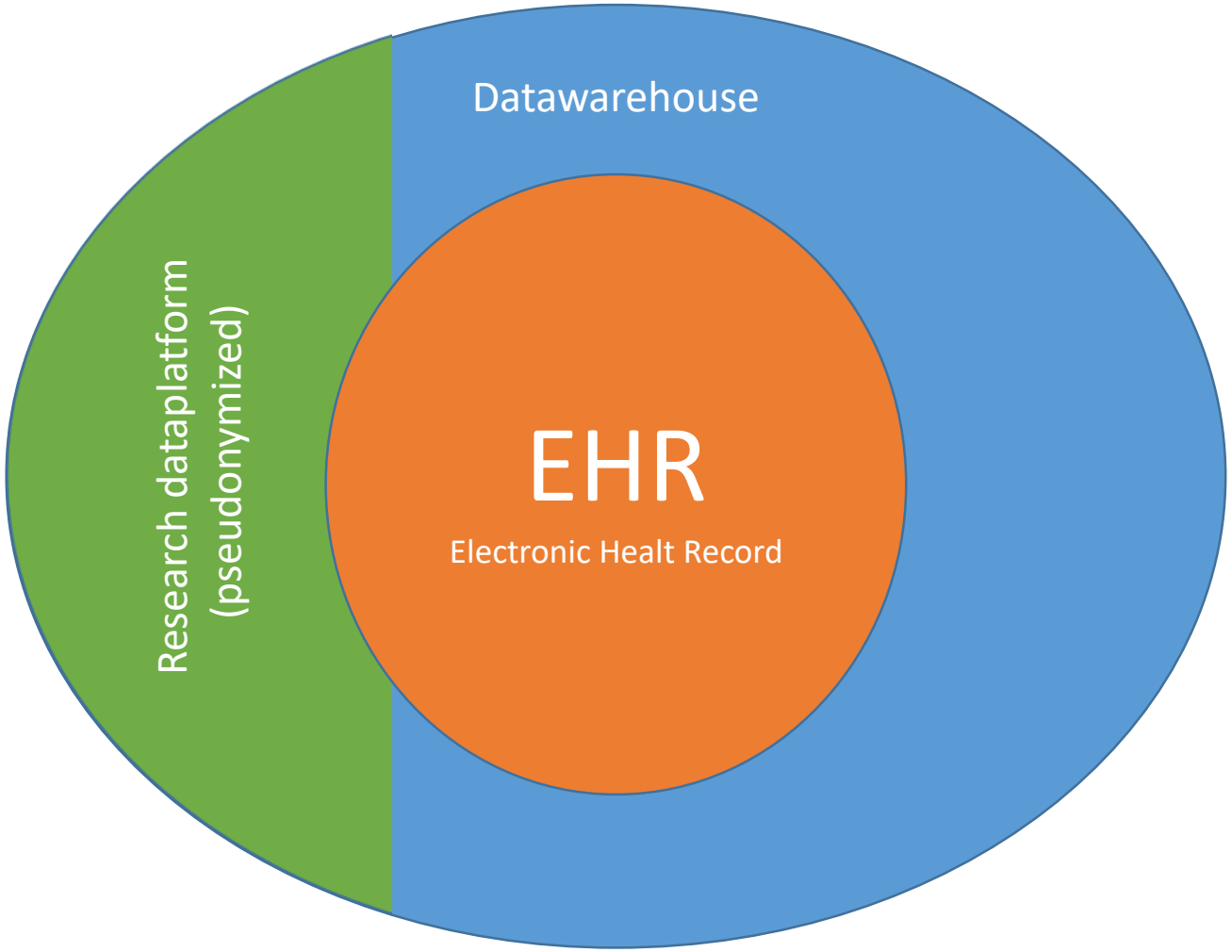
- Ethics of randomization, standardization and uniformation
- <u>Privacy and consent issues</u>

Solutions?

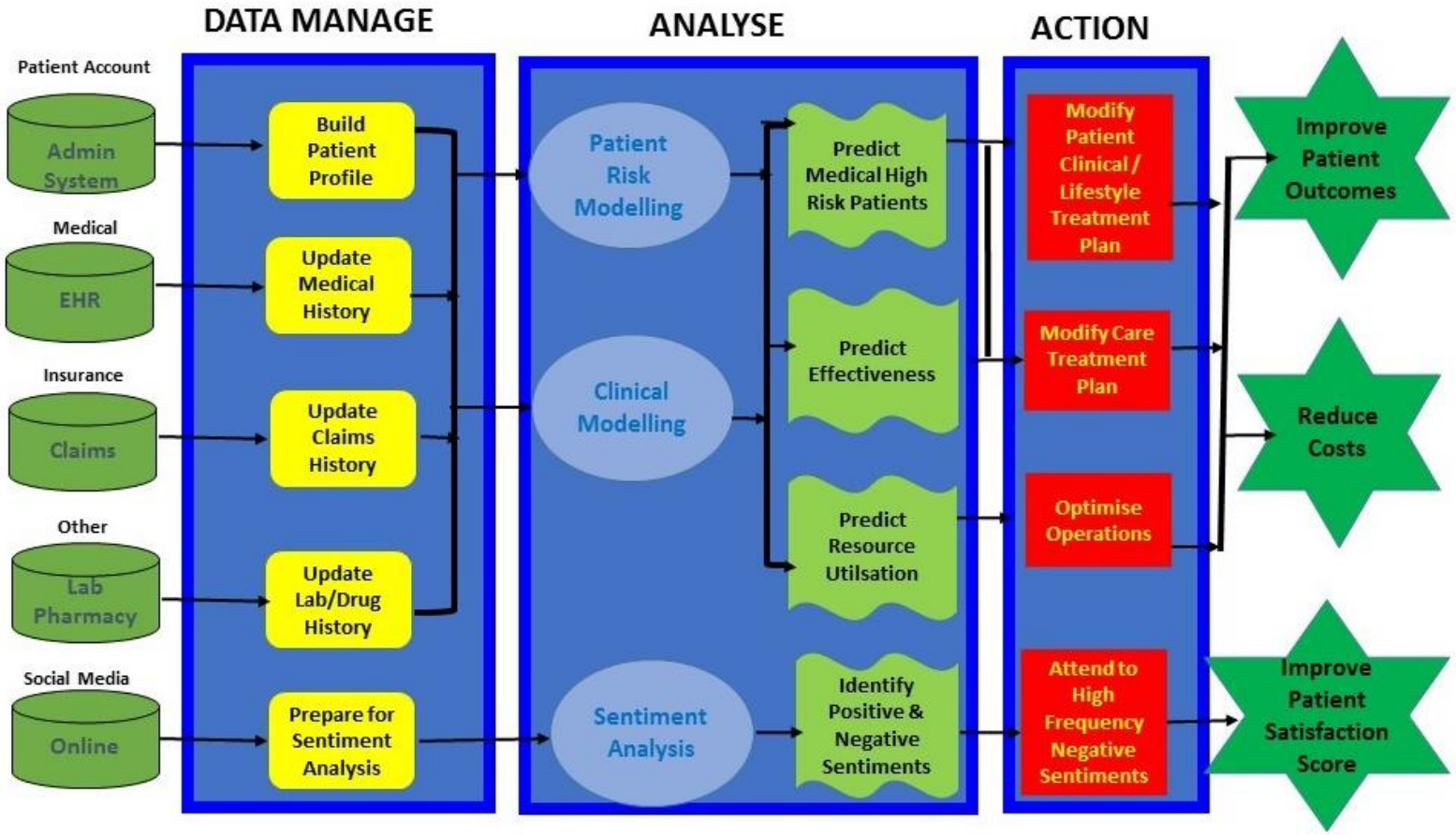
Levels of informed consent



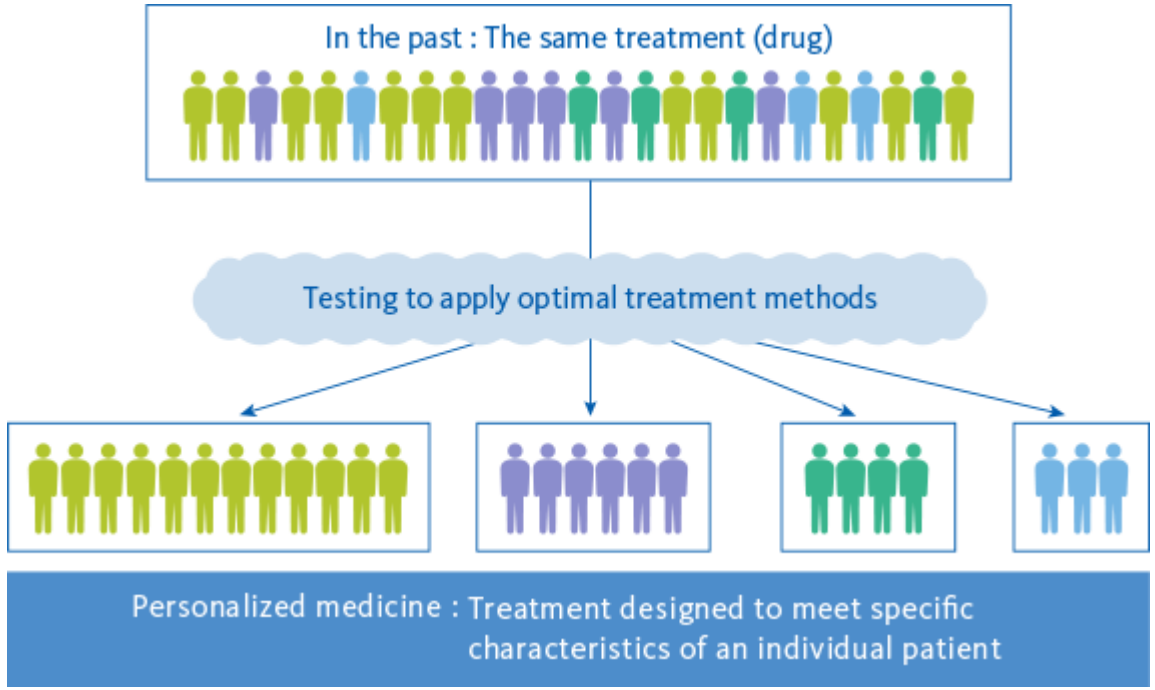
Datamanagement



Data-driven Healthcare



Personalized medicine

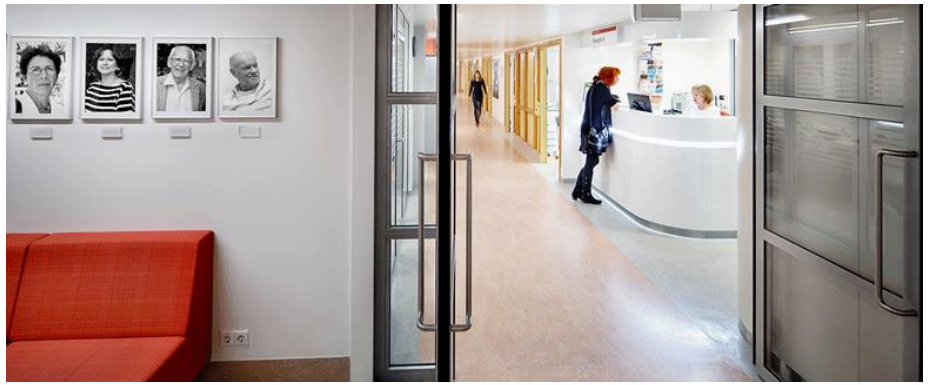


Personalized medicine

To conclude

- Health care and clinical research have different aims, which can cause fundamental frictions.
- Results of clinical research in the past have definitely improved transgender health care.
- Introduction of EHR-systems increase the possibilities for clinical research, but respect for privacy and consent is of utmost importance.
- Intelligent observational designs can reduce the need for standardization and randomisation.

Thanks to



- All people who share their stories in the consulting room

- All participants in ENIGI and ACOG
- All inhabitants of the Netherlands (for serving as reference group)
- All colleagues, PhD’s and students