What is new?

Key findings

In a Learning Healthcare System (LHS) research and care are intertwined in such a way that learning is embedded in the context of care. Its aim by using routine care data (own practice) is to provide evidence with optimal inclusivity of the patient population. Using the example of the Utrecht Cardiovascular Cohort, we show that a traditional informed consent procedure may undermine inclusivity and thus the LHS approach.

What does this add to what is known?

We know that an LHS can potentially provide a more inclusive insight into all patients because care data is collected without restrictions or selections, has a good fit with the true clinical setting, and higher efficiency through use of data that is already collected in routine care. Yet, the obtaining traditional informed consent in an LHS can undermine inclusivity, particularly if a certain patient population is not well represented: the exact opposite of what an LHS tries to achieve.

What is the implication and what should change now?

Modifications of the traditional informed consent process seem essential for LHS when we want to keep an LHS as inclusive as possible. At the same time, these modifications should take into account existing ethical and legal guidance documents for modifications of informed consent. Further research into a new informed consent framework for LHS is needed.

Key words: learning healthcare system, informed consent, routine care data, cardiovascular, electronic patient record, bias

How Traditional Informed Consent Impairs Inclusivity in a Learning Healthcare System: Lessons Learned from the Utrecht Cardiovascular Cohort

T. Katrien J. Groenhof, MD PhD[a] ; Menno Mostert, PhD[a]; Nathan C. Lea, PhD[b]; Saskia Haitjema, MD PhD[c]; Martine C. de Vries, MD PhD[d]; Wouter B. van Dijk MD[a]; Diederick E. Grobbee, MD PhD[a]; Folkert W. Asselbergs, MD PhD [bef]; Michiel L. Bots, MD PhD[a]; Rieke van der Graaf, PhD[a]

a Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

b Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom;

c Laboratory of Clinical Chemistry and Haematology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

d Department of Medical Ethics and Health Law, Leiden University Medical Center, Leiden, The Netherlands

e Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, The Netherlands;

f Health Data Research UK, Institute of Health Informatics, University College London, London, United Kingdom

Corresponding author: Dr. Rieke van der Graaf, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands. E-mail: r.vandergraaf@umcutrecht.nl

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1. Introduction

In 2007, the Institute of Medicine called for the transition of healthcare systems into Learning Healthcare Systems (LHSs), where research and care are intertwined in such a way that daily health care practice is used as a source for continuous learning and that the knowledge that follows from these learning activities accordingly leads to improvement of the health care practice[1] LHSs can take various forms, from first attempts to align research practices with care practices to forms in which randomization is embedded in the clinical setting.[2] The IoMs initiative is more than just a vision on how to streamline research and care. It can also be seen as a moral imperative, in line with the World Medical Association principle in the Declaration of Helsinki that there is "Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality"[3]

In 2014, the Center for Circulatory Health of the University Medical Center Utrecht (UMCU) started the Utrecht Cardiovascular Cohort (UCC) with the implicit, and later explicit, aim to evolve into an LHS.[4] The UCC-Cardiovascular risk management part (UCC-CVRM) is an initiative of all departments in the UMCU that treat patients with a (risk factor for) cardiovascular disease.[4] It aims to improve the quality of electronic health record (EHR) data, provide feedback to physicians on quality of care, and generate new evidence on development and occurrence of disease (aetiology), prediction of development (or recurrence) or presence of disease (prognosis and diagnosis), and therapeutic possibilities including efficacy, safety and cost-effectiveness for cardiovascular disease.[4] In the design of the UCC-CVRM, the researchers focused mostly on the practical integration of medical care and research, which is inherent to an LHS approach. The UCC-CVRM takes the form of what Wouters and colleagues call a “comprehensive data learning health care system”[2] since the UCC-CVRM aims to learn from routinely collected data on a large scale by integrating feedback loops to caregivers. UCC-As such it will move in the direction of what Wouters and colleagues call a real-time LHS, where “real-time feedback of data analysis” is provided “at the point of care”. [2]

The most stringent and perhaps most important characteristic of an LHS approach is the lack of non-participation: every patient that visits the health care system participates, however the current traditional approach to informed consent means that many patients decide not to participate. Non-participation starts when an individual patient is asked for participation in a study or for whether his or her collected (clinical) information can be used for analyses in the context of improvement of health care. In studies into prevalence, incidence, causal relations or prognostic modelling non-participation is usually assumed selective, potentially leading to bias in the frequency measures, such as prevalence and incidence, and/or potentially leading to bias in the measures of associations

(mean differences, odds ratio, risk ratios). Information on the non-participating individuals is generally limited which hampers detailed evaluation of determinants and effects of non-participation on reported findings.

A low informed consent rate is not the focus of this work, rather it is the ethical and procedural issues raised when it is selective – i.e., depends on patient characteristics – that warrants consideration because it may reduce inclusivity – i.e., representativeness of the population- : this has wider implications for participation bias and undermines the premise of the LHS.

Therefore, in this paper we aimed to investigate whether inclusivity of the UCC-CVRM population was at stake with the traditional informed consent procedure as followed by the UCC-CVRM. To be able to explore solutions to the problem of (potential) selective consent, insight is required into how the informed consent process in the UCC-CVROM was designed.

2. The example

2.1. The Utrecht Cardiovascular Cohort

The UCC-CVRM consists of (i) collection of routine care data about cardiovascular risk factor assessment based on Dutch guidelines for Cardiovascular risk assessment, (ii) linkage to other health data sources, and (iii) a biobank.

2.2. Informed consent procedure

Data-intensive LHSs may utilize various approaches to informed consent. When data sets are consist of anonymous data sets, informed consent may be waived. For the UCC waiver of informed consent was not considered an acceptable alternative since patients also were asked to donate a blood sample. All patients receive information about the UCC-CVRM via regular mail at home before coming to the hospital. At the day of the appointment with their healthcare professional, patients are first seen by someone from the medical staff of the department (nurse, medical secretary, physician assistant depending on the department). The UCC-CVRM cardiovascular intake is registered in the EHR, consisting of a questionnaire on medical history, intoxications, physical activity, family history and measurements of blood pressure, height, and weight. Afterwards, patients are asked whether they considered participation in the UCC-CVRM and are counselled according to Good Clinical Practice guidelines. Patients who are invited to participate in the UCC-CVRM are asked for informed consent for ((i) use of their medical data stored in their electronic health records at UMC Utrecht for research by the UCC-CVRM, (ii) collection, storage and use of human material including DNA, and (iii) to inform them about incidental findings. Patients can only

participate in the UCC-CVRM if they agree with all these aspects. In addition, patients provide informed consent to several optional items, such as being approached for future research (Supplement 1). The UCC-CVRM research employees register patients' preferences ("explicit consent plus optional items" or "explicit non-consent") within the electronic health record of the UMC Utrecht. If an informed consent form is not signed for any reason, an "explicit non-consent" is registered for all the informed consent items.

2.3. Results

Up to *July 1st 2019*, *4735* patients were asked to participate in the UCC-CVRM. Out of these 4735 patients, 43% did not provide informed consent. If patients did not consent to participate, the informed consent form was not signed and their non-consent was registered in the electronic health record by the medical staff member as "explicit non-consent" for UCC-CVRM . Consent specifications are shown in Supplement 2, Table 1 (S2T1). Several patients within the explicit consent group opted out for linkage with other healthcare providers (9%) and national registries (15%).

The researchers described differences in risk profile and quality of care between patients that (partially) consented to the UCC-CVRM and those who did not on an aggregate level to obtain an impression on inclusivity of the UCC-CVRM population (ethical waiver for this analysis: Medical Ethical Committee protocol number 19/641). No formal statistical testing was performed. In patients without informed consent, the cardiovascular risk profile was more frequently incomplete compared to patients with informed consent (> 30% less available) (S2T2). Patients who did not provide written informed consent were on average older, more often women, and less educated compared to patients who provided (partial) consent (S2T3). Cardiovascular risk factor levels were more abnormal in patients without consent compared to those with consent. These analyses support the theorem that the current informed consent procedure results in selective non-response, in the case of the UCC-CVRM, a selective non-response of more diseased and frail patients occurred.

3. Discussion

An aim of an LHS for evaluation of care using routine care data (own practice) is to provide evidence with optimal inclusivity of the study population. The traditional informed consent procedures in UCC-CVRM resulted in high rates of non participation and sub-optimal inclusivity of the study population. Patients who did not provide written informed consent were on average older, more often female, and less educated compared to patients who provided (partial) consent.

In the design of the UCC-CVRM, the researchers envisioned that it would incorporate the entire care continuum around a cardiovascular patient and would enable them to answer questions on diagnostics, aetiology, prognosis, and therapy.[4, 5] The informed consent form and procedure as applied in UCC-CVRM might have rightly left patients protected from research in the biobank, but - as shown by our analysis on selective consent - potentially underprotected them from clinical errors and suboptimal management as subgroups do not contribute to the LHS and the researchers now cannot provide feedback on quality of care to the treating physicians on these patients.[6] Amongst other things, that traditional informed consent procedures actually can hinder LHS aims may support the need to change the conventional consent criterion in an LHS.

The informed consent policy and procedure, as followed in the UCC-CVRM, was found to be in accordance with legal and ethical standards by an ethical review committee of the UMCU. For the collection and use of materials for biobanking purposes, a written informed consent from the patient is required. For the use of routine care data in research or linkage of health data sources, explicit consent from all patients included is in principle required. Dutch law contains exception clauses which allow to waive the informed consent criterion for the use of health-related personal data for scientific health research purposes, even when it involves information covered by the duty of professional medical secrecy. These exceptions from the consent criterion apply when obtaining explicit consent either proves to be impossible or requires a disproportionate effort. Furthermore, additional requirements must be met: the research serves a public interest and proportionate protective measures, such as pseudonymisation, need to be taken.[7,8] When the researchers set up the UCC-CVRM and submitted the protocol to the ethical review committee, they thought that there was a *reasonable* opportunity to obtain traditional informed consent from the patients. Thus, their perception was that it would be feasible to obtain informed consent and hence that applying a consent waiver was not appropriate. However, in hindsight this perception was incorrect. To obtain explicit informed consent for the sole use of health data seems to make it impossible to achieve the objective of an inclusive LHS.

The legal and ethical requirements that form the basis of the informed consent policy and procedure, as followed in the UCC-CVRM, are often reported to be burdensome, confusing or open to interpretation.[9-11] The recent advent of the General Data Protection Regulation (GDPR) has further raised questions and concerns related to the reuse of personal data for health research and other purposes.[12,13] However, it has been pointed out that because of the complex regulatory landscape, existing flexibilities in the law to address regulatory hurdles are often overlooked in

practice.[10] The GDPR also provides such flexibilities, for instance by providing other legal bases than informed consent for the use of personal data in care, health service management and scientific research, and by allowing for a care, management and scientific research exception from the prohibition to process sensitive personal data in the public interest.[14,15] In other words, the GDPR does not necessarily require informed consent for the use of (sensitive) personal data in scientific research. Moreover, it is suggested that informed consent may not be the most appropriate legal basis for processing this data, particularly in large-scale epidemiological or genetic studies.[16] GDPR mandates transparency about the processing of personal data, which supports well established informed consent processes for research and procedures around using health records for care and service management

The form of informed consent within an LHS has been systematically reviewed by Cumyn et al., emphasizing the need to assess societal acceptance and the importance of the explanatory conversation between patient and health care professional.[17] A more lenient approach to informed consent is also in line with the *"Ethics Framework for a Learning Health care System"* that was developed by Faden and colleagues in 2013.[18] They argue that ethical assessment and informed consent requirements for an LHS should be proportional to the complexity of the learning activity and potential risks that come with the learning activity.[18] A learning activity is defined *as "an activity… that both (i) involves the delivery of healthcare services or uses individual health information, and (ii) has a targeted objective of learning how to improve clinical practice or the value, quality, or efficiency of systems, institutions, and modalities through which health care services are provided".*[18] The learning activity risks include the prognosis on clinical outcomes, such as myocardial infarction or death, but also religious and moral arguments associated with the clinical outcomes. Reviewing could include a prominent role for a patient panel.[18]

When health data is reused for a wider purpose than care, another challenge on top of the ethical and legal legitimacy of data use arises: trust. The trust of patients in the integrity and quality of medical care and research is based on awareness and understanding of the use of their data.[19] The *care.data* project, an abandoned initiative that extracted data from primary care health records for research aims, based on an opt-out and following established regulations at that time, illustrates this well. The lack of awareness of the projects goals in addition to the complexity of the opt-out procedure, resulted in distrust, concern and controversy among patients: a "social license" for the project was absent.[19] Social license is the expectation built on the value of privacy, confidentiality, interests and relevance, concerns about stigma, and religious and moral objections.[20,21] Though the law aims to meet some of these expectations, the social license is an additional lens on how to

manage relevant expectations irrespective of consent requirements or other regulations. To this extent, transparency on medical data use for research and involvement of patients in (ethical) assessment of these learning activities is essential.[22]

The challenges with informed consent for the UCC may not apply to all LHSs, particularly those that are less "data-intensive". For example, it is conceivable that consent rates would be higher if participation did not also simultaneously include the blood draws and biobanking.

In summary, we cannot fully reap the benefits of LHSs if we keep traditional informed consent procedures in place. We believe that modifications of the traditional informed consent process are essential for an LHS with a view to inclusivity, while taking into account existing regulations and well-established ethical values in the context of data research such as trust. Further research into a new informed consent framework for LHS is needed.

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Competing interests

The authors declare that there are no competing interests.

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Author contributions

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Supplement 1 - Original Informed consent Utrecht Cardiovascular Cohort

Informed consent Utrecht Cardiovascular Cohort (UCC)

- ✓ I have read and understand the participant information for participation in the UCC. I had the opportunity to ask questions. These questions have been answered. I have had enough time to think about participation.
- ✓ Participating in the UCC is completely voluntary for me.
- ✓ I am aware that I have the right to withdraw my consent at any time without explaining why and I know that this will not have a negative impact on my medical care.
- ✓ Persons other than the healthcare professionals that take part in my care process and the hospital may conduct research with my medical data and body material (including DNA).
- ✓ I understand that the medical data and body material are stored without my personal data, so that it is not known to the person carrying out the research that the medical data and body material originated from me.
- ✓ I am aware that some people can review my data. People who can review this data are people from the research team and people who check whether the research is being carried out properly and reliably.

I am participating in this study and

- ✓ *I consent to the use and storage of my medical data recorded in patient records at UMC Utrecht for research by UCC.*
- ✓ *I consent to the collection, use and storage of human material (including DNA) for research at the UCC.*
- ✓ *I know that individual findings that are important to me will be reported to me.*

- ✓ *I consent to contact me for participation in other studies in the future.*
  ☐ yes ☐ no

- ✓ *I consent to future retrieval of medical information from my doctor, pharmacy and other hospitals where I have been treated in the past, in the interest of the UCC.*
  ☐ yes ☐ no

- ✓ *I consent to future request to link with various ((inter)national) registrations in the interests of the UCC, such as: Municipal Basic Administration (GBA), Central Bureau of Statistics (CBS), Dutch Cancer Registration (NKR), Foundation for Pharmaceutical Statistics (SFK), RENINE (Dutch Kidney Function Replacement Foundation), National Basic Registration of Hospital Care (LBZ), Regional ambulance services, Vektis (about the use of care) and other regional and national registrations.*
  ☐ yes ☐ no

- ✓ *I consent for research in collaboration with profit-making companies with my medical data and body material.*
  ☐ yes ☐ no

- ✓ *I consent to contact me by e-mail for UCC.*
  ☐ yes ☐ no

Supplement 2 – Detailed results in tables

Table 1. Detailed informed consent distributions of patients eligible for UCC

	Number of patients (%) **Total n = 4735**
Explicit non-consent	2036 (43%)
Explicit consent	2699 (57%)
To contact me for information/ participation in future studies	2690 (99.7% of 2699)
To link my data with other healthcare provides	2456 (91% of 2699)
To link my data with (national) registries	2294 (85% of 2699)
To use my data in cooperation with a commercial party (industry)	1244 (74% of 1692*)
To contact me by e-mail	1409 (83% of 1692*)
Consent for all above	2267 (84% of 2699)

* this question was added in the second version of the consent form and therefore answered by 1692 patients. For that reason percentages could also be lower than 84% (consent for all)

Table 2. Availability of cardiovascular risk management guideline information in the routine care electronic health records.

	With consent	Without consent
SBP present (%)	93	87
DBP present (%)	93	87
BMI present (%)	93	87
Smoking status present (%)	95	65
CVD history present (%)	96	65
Hypertension history present (%)	96	65
Creatinine present (%)	87	82
Total cholesterol present (%)	83	74
HDL-c present (%)	82	73
Hb present (%)	87	82
CVD 10-years risk estimation present (%)	74	45

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; CVD = cardiovascular disease; HDL-c = high density lipoprotein cholesterol; Hb = hemoglobin

Table 3. General characteristics of the studied population, in strata of those with and without written informed consent.

	With consent		Without consent	
	Mean	SD	Mean	SD
Age in years at baseline	58.38	17.58	65.96	18.10
Women (%)	48		55	
High education (%)	41		29	
Current smoker (%)	12		13	
Previous CHD, stroke, AAA, PAD (%)	34		38	
Hypertension (%)	47		50	
Kidney disease (%)	17		17	
Proteinuria (%)	15		10	
Diabetes (%)	21		20	
Hyperlipidemia (%)	39		35	
Body Mass Index (kg/m2)	26.88	5.76	26.36	5.11
Heartrate (bpm)	73.49	14.08	75.29	14.76
Systolic arterial blood pressure (mmHg)	139.43	22.88	144.50	25.59
Diastolic arterial blood pressure (mmHg)	79.72	12.13	79.92	12.51
Total cholesterol (mmol/L)	5.20	1.43	5.15	1.32
HDL-Cholesterol (mmol/L)	1.38	0.41	1.38	0.39
Hb (mmol/L)	8.72	0.97	8.47	1.05
Creatinine (µmol/L)	85.23	50.77	92.03	82.11
eGFR (CKD epi)	83.58	24.75	76.56	26.36
HbA1c (mmol/mol)	40.12	11.64	41.45	12.15
Use of medication (%)	86		90	
10 year risk on morbidity/mortality by CVD (%)	22.56	24.24	27.04	26.41

Abbreviations: SD = standard deviation; CHD = coronary heart disease, PAD = peripheral artery disease, AAA = aneurysm of the abdominal aorta; HDL = high-density lipoprotein, Hb = hemoglobin, eGFR = estimated glomerular filtration rate according to the CKD-EPI formula, HbA1c =glycated hemoglobin; CVD = cardiovascular disease

Competing interests

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