Does point-of-care ultrasound examinations by the general practitioner lead to inappropriate care? A follow-up study.

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# Author contributions

CAA is the principal investigator of the GULD study and this follow-up study. JB, JLT, TL, OG, JM and MBJ have contributed to the concept, design and drafting of the protocol. JB, MBJ, and JM will be conducting the review and assessment of patients’ medical records, and OG conducted the assessment of the participating GPs technical POC-US skills. CAA and MBJ will be conducting the data analysis. All authors revised critically and approved the final manuscript of the protocol.

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# Background and rationale

Ultrasonography (US) is increasingly used as a bedside point-of-care examination (POC-US)[[1]](#endnote-1). Previous research supports that this use of US leads to earlier and more correct diagnoses in hospitalized patients[[2]](#endnote-2) [[3]](#endnote-3). However, the long-term effect on morbidity and mortality has not been proven[[4]](#endnote-4). The increased use of POC-US by clinicians has raised concerns about the quality and effect on patient care. POC-US is a user-dependent technology and therefore entails the risk of misinterpretation leading to mistreatment. Furthermore, an increased usage of imaging may lead to overdiagnosis, spurious findings or the diagnosis of clinical unimportant conditions[[5]](#endnote-5) [[6]](#endnote-6).

Literature on the use of POC-US in general practice is sparse and there is a lack of high quality studies. A recent literature review[[7]](#endnote-7) has shown that focus in previous research have been given to the training of GPs and the diagnostic accuracy of the performed US examinations. Less attention has been given to the patient’s clinical pathway succeeding the US examination in the GP’s office and the number of adverse events following the use of POC-US in general practice. However, misdiagnosis in terms of false positives and false negatives were described in 17% and 16% of the included papers respectively whereas incidental findings were described in 20%. Hence, US in general practice might cause harm to patients.

Therefore, we need estimates of potential unintended harms to patients, when GPs perform POC-US. This may be obtained by retrospectively evaluating the medical records of patients who have been scanned by their GP. In a recent prospective cohort study from our unit (Clinical trials registration number: NCT03375333) we included patients who had had POC-US performed from 20 GPs. An evaluation of their clinical pathways would allow an estimate of adverse events related to POC-US by their GP.

The classification of adverse events has previously been used to describe harms following an intervention and an international standard (EN 540/ISO 14155) has been developed for identifying adverse events in clinical trials (kilder). Using this standard, we will be able to systematically identify the number of adverse events described in the patients’ medical records. An expert panel will be evaluating these events in terms of causality and seriousness in order to characterize and describe the possible harms following use of POC-US in general practice. Furthermore, we will be able to evaluate the clinical consequences during the subsequent six months of the incidental findings identified at the initial scanning.

The aim of this study is to describe the POC-US related adverse events and incidental findings identified through a six months follow-up evaluation of medical records of patients having undergone POC-US by their GP.

# Objectives

## Primary outcome

To determine the incidence of serious adverse events on patients in general practice related to the POC-US examinations performed by their GPs (Serious adverse device effect, SADE) identified in a six month follow-up evaluation of medical records.

## Secondary outcomes

Using the same method, our secondary outcomes are to determine:

The incidence of adverse events ***related*** to GP performed POC-US examinations on the general practice patients:

* Possibly serious adverse device effects (pSADE)
* Adverse device effects (ADE)
* Possibly adverse device effects (pADE)

The incidence of adverse events ***not related*** to the POC-US examinations that was done by the GP on the general practice patients:

* Serious adverse events (SAE)
* Adverse events (AE)

## Tertiary outcomes

By combing the classified SADE, pSADE, ADE, and pADE with data registered in the GULD study (GP questionnaire and background information on the participating GPs), our tertiary outcomes are to describe the frequency of SADE, pSADE, ADE, and pADE for each of the following:

* Organ examinated with POC-US
* Change in the GP’s management of patient after POC-US (Change in diagnosis, change in plan, change in treatment)
* Uncertain POC-US findings (uncertain positive findings, uncertain negative findings)
* Technical skills of the general practitioner (OSAUS score)
* Type of ultrasound device used (low-/high end)

In addition we will describe the identified SADE, pSADE, ADE, and pADE in order to determine if the POC-US examination by the GP lead to inappropriate care:

* Incidence of misdiagnosis of patients (False positives, false negatives and misclassification) by the GP at the consultation where POC-US was initially performed.
* Incidence of mistreatment of patients by the GP at the consultation where POC-US was initially performed.
* Incidence of potential overdiagnosis

And finally we identify, classify and describe incidental findings.

# .Trial design

Prospective cohort study

# Method

## Study setting

Data for this follow-up study originates from the prospective cohort study: “How Point-of-Care Ultrasound Affects the Diagnostic Process in General Practice” (Clinical trials registration number: NCT03375333) with the working title: *GULD study*. The cohort study took place in general practice clinics during 2018 and each participating GP included patients for one month. This follow-up evaluation of the included patients’ clinical course will be conducted at the Center for General Practice at Aalborg University.

## Eligibility criteria

**Participating general practitioners**

The participating 20 GPs were selected based on difference in general practice organisation, geography, equipment, and experience both regarding seniority as GPs and experience in using POC-US. However, they had to have at least one year experience with using POC-US, have taken some course to learn to scan, and to use POC-US in at least two anatomical areas on a daily basis.

**Participating patients**

All patients who consulted a participating GP for a condition that the GP found relevant for a POC-US examination were offered to participate in the study. Patients were excluded if they did not wish to participate or if they were not able to give an informed consent.

Patients could only be included once and only patients on the general practice’s list could participate in the study. The GPs included between 12 and 70 patients, resulting in a total of 577 patients.

**Participating student reviewers**

Two medical students will be invited to participate in order to review the prints from the included patients’ electronic medical records in order to identify AE related to the health complaint raised in the first consultation. We will pilottest the students abilitities to perform the review.

**Participating expert reviewers**

Two expert GPs with extensive experience in both research and quality insurance in general practice will review the prints of the medical records in those with adverse events to further classify the type of adverse events and describe causality. A third expert with extensive experience in quality evaluation of clinical pathways will be invited to settle any disagreement regarding classification in discussion with the two expert GPs.

## Interventions

There is no intervention as this is a follow-up study of patients, who have all been scanned. This study does not add any examinations of patients or in other ways influence the treatment of patients.

## Outcomes measures

### **Primary and secondary outcome measures**

### For the primary and secondary outcomes the patients’ electronical medical records are reviewed in two rounds in order to identify and classify adverse events according to international standard EN 540/ISO 14155 (https://www.iso.org/standard/45557.html) classification of adverse events for medical devices:

**Adverse Event (AE)**

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device (POC-US examination in general practice).

**Serious Adverse Event (SAE)**

Adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or

- a permanent impairment of a body structure or a body function, or

- in-patient hospitalization or prolongation of existing hospitalization, or

- in medical or surgical intervention to prevent life threatening illness

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

**Adverse Device Effect (ADE)**

Adverse event related to the use of an investigational medical device (POC-US examination in general practice).

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device (POC-US examination in general practice).

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device (POC-US examination in general practice).

**Serious Adverse Device Effect (SADE)**

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Figure 1: Adverse event categorization chart (ISO 14155:2011):

Adverse event

AE

No

Is the event device or procedure related?\*

Does the event meet seriousness criteria?

Yes

No

\* causality analysis is performed according to The European Commission’s guideline on medical devices. The relationship between AE and POC-US is categorized as being not related, unlikely related, possibly related, probably related or causal related.

Yes

Yes

SADE

Is the event device or procedure related?\*

ADE

SAE

### **Tertiary outcome measure**

For the tertiary outcomes we will include the following data from the GP questionnaire in the GULD study:

* organ scanned

The ***organs scanned*** are registered before and after POC-US on a list of organs in the GP questionnaire. The possibilities in this list originate from interviews with GPs using POC-US and from pilot testing. The GPs could choose to write in free text if organs are missing from the list. We will include the organs registered after POC-US.

* Change in the GP’s management of patient after POC-US

After POC-US the GPs registered if their tentative diagnosis had changed, if their plan for the patient had changed, and if their treatment of the patient had changed.

* POC-US findings

After POC-US findings were measured through the categorial variables *certain* *positive findings, un*certain *positive findings, certain negative findings, uncertain negative findings, and incidental findings.* We will test the association between POC-US related AE and Uncertain findings (*un*certain *positive findings and un*certain *findings)* and *incidental findings.*

The following data was registered as background information of the participating GPs in the GULD study.

* technical skills of the general practitioner (OSAUS score)

The participating GPs had their technical POC-US skills assessed at baseline. Each participating GP was asked to perform POC-US in a standardized setting and reviewed by an external reviewer (radiologist) using the standardized protocol[[8]](#endnote-8), providing an OSAUS score for each participating GP.

* type of ultrasound device used (low-/high end)

Participating GPs were asked to describe their US device and the research team categorised these as high-end, mid-range or low-and US devices.

## Participant timeline

Table1 illustrated the expected timeline for this study.



## Sample size

The sample size is determined by the number of patients included in the GULD study as this is an extension of that study. It is anticipated that 577 patients will be included.

## Recruitment

## Participating GPs:

We use data from the GULD study. GPs in the GULD study were recruited through the continuous medical education small-groups program, US networks, conferences, through teaching sessions, and through contacts via the Danish general practice research units.

## Participating Patients:

All patients in the GULD study were asked if they wished to participate in this follow-up study. Patients with a signed informed consent form will be included in this study.

### **Participating student reviewers**

The two medical students will be selected based on their interest in general practice and their research experience.

**Participating expert reviewers**

Three expert reviewers will be purposively selected. Two reviewers will be GPs and professors in general practice. One of the two GPs will have several years of experience in using POC-US in a general practice setting (MBJ), whereas the second GP will have extensive experience in the field of overdiagnosis and overtreatment (JB). The third expert, who will settle any disagreement regarding classification of AEs through discussion, has great clinical and scientific knowledge in quality assurance.

## Data

**GP questionnaire:**

During the GULD study GPs have electronically registered diagnoses, plan, type of examination, and findings for each patient before and after POC-US. We will identify patients where the GPs have registered incidental findings, change in plan or treatment for the patients. A list with the unique patientID of the identified patients will be included for the second-round review of medical records.

**Patients’ medical records**

All included patients arelisted with a participating GP and the GP will as standard care and communication, receive notice of all health events regarding a patient on the list, e.g. lab results or discharge notices. These data will automatically be uploaded to the electronic medical record. This data will be used for the evaluation of the clinical course of the patient including assessing if any AE has occurred.

## Collecting data

The data collection is described in the protocol for the GULD study (“How Point-of-Care Ultrasound Affects the Diagnostic Process in General Practice. A prospective follow-up study” Clinical trials registration number: NCT03375333)

Participating GPs will print all data from the electronical medical records of the participating patients from the time of the initial consultation with POC-US (Inclusion in the GULD study) and six months forward. The names and CPR numbers (a unique national identification number in Denmark) will be removed and replaced by the patientID number used in the GULD study. The GPs will also be given the opportunity to save anonymized patient data on a USB stick.

The data are picked up from the GPs office by an employee from the Center for General Practice in Aalborg or hand-delivered to the research unit by the participating GP.

##  Data evaluation

**Review of the patients’ medical records**

The review process of the patients’ medical records will follow the following steps:

Data handled by:

General practitioners

Student reviewers

Expert reviewers

Research group

**First review round**:

Two medical students will individually review all the prints from the patient’s electronic medical record from the initial consultation regarding the primary health complaint where POC-US was performed and six months forward.

Patients with no additional information after the initial consultation are classified as not having experienced any AE. Patients with subsequent data in the medical record will be classified as having had an AE related, possibly related or not related to the primary health complaint. All patients identified by one or both student reviewers as having AE related or possibly related to the primary health complaint will moved on to the second review round. Patients identified by both student reviewers as having no AE related to the primary health complaint will be reviewed by one of the expert reviewers to ensure all patients with AE related or possibly to the primary health complaint are identified.

**Second review round**:

Two expert reviewers will independently assess the medical records of patients having an AE related to the primary health complaint.

The AEs are then classified according to the events’ seriousness according to the EN 540/ISO 14155 (Figure 1) and secondly the relationship between the AE and POC-US is described using the categories described in The European Commission’s guideline on medical devices (CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC). The relationship between AE and POC-US is categorized as being *not related*, *unlikely related* ( the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause), *possibly related* (the relationship is weak but cannot be ruled out completely), *probably related* (the relationship seems relevant and/or the event cannot reasonably explained by another cause) and *causal related* (event is associated with the investigational device or with procedures beyond reasonable doubt). Information from the GP questionnaire concerning patients with incidental findings, and patients where the POC-US lead to change in plan or treatment for the patient as well as the patient’s assessment of the POC-US consultation are available for this causality analysis. Finally, the adverse events are classified according to the EN 540/ISO 14155 standard as AE, SAE, ADE and SADE. For this classification events with no relationship to POC-US includes *not related* and *unlikely related,* and events with a relationship to POC-US includes *probably related* and *causal related*. Hence, events classified by the experts as *possibly related* to POC-US adds the categories possibly adverse device effect (pADE) and possibly serious device effect (pSADE).

Incidental findings registered in the GP questionnaire or identified during this second review round, will be classified and described according to their net benefit[[9]](#endnote-9) as either having a *Strong Net benefit* (important incidental finding revealing a condition likely to be life-treatening or grave, that can be avoided or ameliorated), *Possible Net Benefit* (incidental finding revealing a nonfatal condition that is likely to be grave or serious but cannot be avoided or ameliorated) and *Unlikely Net Benefit* (incidental finding reveiling a condition that is not likely to be of serious health or reproductive importance e.g. dectection of a US findings of doubtful clinical significance recorded by the GP at the consultation where POC-US was initially performed and sustained as of doubtful clinical significance at the evaluation after six months).

A third expert reviewer will be involved in the assessment to settle any disagreement between the two assessments at each step.

After the causality analysis the three reviewers will make a joint narrative description of the identified POC-US related adverse events (ADEs and SADEs) as well as the possibly POC-US related adverse events (pADEs and pSADEs) and incidental findings.

## Data management

All data will be handled according the General Data Protection Regulation and national Danish Laws – monitored by the Danish Data Protection Agency.

The Research Unit for General Practice in Aalborg is the Data Controller. Each participating GP will be data processor and can only process data pursuant to an agreement with the data controller. A data processor agreement will be made between the Research Unit for General Practice in Aalborg and each participating GP, between the Research Unit for General Practice in Aalborg and Aalborg University, and between Aalborg University and SurveyXact according to the Danish Data Protection Agency recommendations.

##  Statistical methods

For our primary and secondary outcomes we will describe the identified adverse events in absolute frequencies. For our tertiary outcomes we will use absolute frequencies tables and chi-square or Fishers exact test to test the relationship between variables.

**Ethical approval**

The Danish National Committee on Health Research Ethics have been consulted and declared that approval by this committee is not needed. The GULD study and this follow-up study have been approved by the Danish Data Protection Agency (no. 2017-41-5273) and the Committee of Multipractice Studies in General Practice (no. MPU-20-2016).

**Consent or assent**

Prior to participation in the GULD study and this follow-up study patients received written and oral information and a written consent to participate was obtained by the participating GP. Patients may redraw their consent at any time until data is anonymized and forwarded to Center for General Practice at Aalborg University (after six months). Patients withdrawing consent will stop providing data.

**Confidentiality**

All participating GPs and researchers will sign a confidentiality agreement.

**Declaration of interest**

All participating GPs and researchers will sign a conflict of interest form

**Access to patient data**

The printed copy of the electronic medical record will be will be kept in a locked safe in a restricted access area. It will be accessible for the researchers assessing the adverse events. Following the review process the papers will be scanned to a pdf file. This pdf file will be safely stored in an electronic repository at Center for General Practice at Aalborg University together with other project data.

The data will be saved at a server in Aalborg University. Only the principal investigators in the research unit for general practice in Aalborg (CAA, MBJ, JLT) will have access to this data using two unique passwords.

The patient key file connecting this patient-ID to the patients name and CPR number as well as the signed consent forms will be saved locked up at the GPs’ office and the research group will not have access to this information during the study.

**Dissemination policy**

The knowledge of this study will be disseminated through conferences, research networks, and papers published in peer reviewed journals.

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