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TITLE: From hospitalization to primary care, integrative model of clinical pharmacy with patients implanted with a PICC line: research protocol for a prospective before-after study.

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Trial acronym: CLIPICC

Abstract

Introduction

Clinical pharmacy is an efficient, patient-centered discipline that significantly improves the safety of drug management. However, concerning medical devices, studies are not yet numerous. Clinical pharmacy applied to medical devices seems to be unexploited and proof of effectiveness is needed. We hypothesize that clinical pharmacy applied to medical devices could be as effective as in the medication field.

Aim

The main objective is to assess the effectiveness of clinical pharmacy activities during entire care pathways of patients implanted with a PICC line.

Methods

This is a before-after and prospective study. The study will begin with an observational period, followed by an experimental interventional period. Sixty-nine adult patients in each period will be recruited. Inclusion criteria will be the implantation of a PICC line, a return home project and the ability to be called by phone for a 3-months follow-up after discharge. During the observational period, no clinical pharmacy activities will be performed. During the interventional period, clinical pharmacists will be active throughout the entire patient's care pathway: from the onset of PICC line prescription to primary care. The primary outcome will evaluate the effectiveness of clinical pharmacy in reducing the number of complications per patient per month. Secondary outcomes will evaluate the impact on consultation and hospital readmission rates, the acceptance rate of pharmaceutical interventions, the impact on patients' quality of life, the direct hospital induced or avoided costs and the satisfaction of every participants.

Discussion

This study aims to assess the number of PICC line complications by month at baseline and after clinical pharmacy activities. Each step of care pathway of patients is targeted, from hospital to

primary care. Regular phone calls to the patients allow for close monitoring and the follow-up at home.
This is a preliminary study to establish initial results before considering a larger, randomized and multi-center study.

Trial registration

2019-A02475-52 (ID-RCB number)
Ethics Committee Number: AU1586 (Clermont-Ferrand Southeast VI, France).
ClinicalTrials.gov: not yet applicable

Keywords

Clinical Pharmacy, Medical Devices, PICC lines, Protocol, Before-After Study

Strengths and Limitations

- Unfortunately, randomization is not possible due to the high risk of contamination bias and the financial cost of cluster randomization exceeds our budget.
- Due to the nature of the clinical intervention (e.g. pharmaceutical interviews), blinding is not possible for patients nor for healthcare professionals.
- This is the first study to assess the effectiveness of clinical pharmacy applied to medical devices.
- This study propose an integrative model of clinical pharmacy, beyond hospitalization, that promotes multidisciplinary work and collaboration with primary care.

Introduction

Clinical pharmacy is a pharmaceutical discipline in its own right. Described for the first time in the 1960s, clinical pharmacy today is defined as a patient-centered health discipline whose practice aims to optimize therapy at each stage of the care pathway. Clinical pharmacy actions contribute to the patient safety and the relevance and efficiency of the use of health products (1). Clinical pharmacists can occupy a privileged position in delivering enlightened information to patients (2) and being the link between the hospital and the patient's home. The hospital activity of clinical pharmacy is regulated by law in many countries and especially in France (3,4). Its execution is mandatory and is becoming a priority among other missions, especially in rural areas (5). Clinical pharmacists are part of the medical staff and practice in collaboration with the other healthcare professionals.

Regarding pharmacological approaches, the effectiveness of clinical pharmacy is well known and several clinical studies demonstrated significant impact on the decrease of the number of re-hospitalizations at 30-days (6–9) together with other measures such as therapeutic assistance (10) and a decrease of iatrogenic risk associated with inappropriate prescriptions or medical discrepancies (11–14). Some studies also show a significant improvement in treatment adherence (15) and sometimes an enhanced quality of life for patient with chronic heart failure (16). Regarding medical devices (MDs) more specifically, studies concerning clinical pharmacy are rare (17). Studies involving pharmacists demonstrated improvements in ergonomic assessments and operator's convenience of use, as well as the organizational impact (18) with surgeons and in the operating room. However, to our knowledge, nothing describes the clinical impact of pharmacists' intervention with patients who use or carry MDs. Only one recent article refers to medication reconciliation, which represents one single step in the patients' course, for those with dressings for complex wounds (19). In light of this fact, the need of clinical studies is undeniable to explore the effectiveness of clinical pharmacy over the entire patient care pathway including MDs use.

Clinical pharmacy activities begin in the hospital (20) and must continue after patients' discharges(21). Considering the entire patient's care pathway is effectively a priority for the improvement of efficiency and appropriateness of care. Currently, multidisciplinary teamwork is necessary, both within the hospital care setting (22) and with primary care (23). Communication and collaboration centered on the care pathway need to be further strengthened in order to be more effective. In literature, nurses and hospital teams have produced a great deal of work. Transitions between different care structures are recognized as the most risky steps in patient management(24,25). Late discharge letters delay the communication of information to primary care (26), and discrepancies in prescriptions(27) are one of the causes of avoidable errors. To our knowledge, concerning MDs, nothing includes pharmacists, whose efforts focus on the risks of these transitions. We hypothesize that clinical pharmacy could reduce these risks in the entire care pathway for patients implanted with MDs.

Medical device category is a very broad and heterogeneous group of healthcare products, from bandages to magnetic resonance imaging machines. MDs are classified according to the risk inherent in their use for the patient. The risk is assessed according to the invasiveness, duration of use and the anatomical purpose of the MD. These different criteria make it possible to differentiate four classes: I, IIa, IIb and III, whose risk for use increases with the class. Infusion equipment, such as catheters, is known to be responsible for iatrogenic events, especially infections (28,29). We chose the PICC lines in our study because of the variety of studies about complications rates, both at the hospital (30–38) and at patient's home (39–45). PICC lines are commonly used peripherally inserted central catheters. They are implantable MDs (class III, mandatory health traceability)(46). PICC lines are recommended for irritating products administrations such as long-term antibiotic therapy, cancer chemotherapy and parenteral nutrition or iterative blood samples when the venous capital is fragile. PICC lines are recommended when the duration of catheterization goes from 7 days to 3 months (47). PICC lines are placed in the interventional radiology operating room by radiologists or residents.

We aim to deploy clinical pharmacy interventions in every step of the care pathway of patients implanted with a PICC line, from hospital admission to primary care through a follow up of 3 months.

We are going to propose a coordination and communication between hospital prescriber, operating room, hospital nurses as well as primary care which involves nurses, physicians, pharmacists and patients themselves through phone calls to track clinical complications at home during the whole period of implantation. The primary outcome is to decrease post-procedural complications after PICC line implantation through clinical pharmacy activities. We also want to rationalize the organization of care by focusing on the optimization of the logistic circuit, to improve professionals' coordination and communication, to encourage the pharmacist's integration in the multidisciplinary team and introduce the concepts of clinical pharmacy of MDs.

Design & Methods

A scientific committee (selected by the Research and Innovation Board of the Toulouse University Hospital) composed of scientific and methodological experts oversaw the feasibility and methodology of the study. Thus, this committee ensures the quality and relevance of the research organization.

The study procedures and assessments respect the Standard Protocol Items: Recommendations for Interventional Trials(48).

Aim

We hypothesize that the interventions of the clinical pharmacist at each stage of the management of a patient implanted with a PICC line should help prevent complications. Moreover, we hypothesize that clinical pharmacy should reduce the number of rehospitalizations and physician visits, thereby reducing hospital costs.

Design

The study consists of two consecutive phases: observational (no clinical pharmacy activities) and interventional (execution of clinical pharmacy activities and logistic optimization).

A simple center before-after design is suggested. The cluster method is not possible in our hospital due to its division by sites and activities. This would expose us to a selection bias: participants would not be comparable in terms of reasons for hospitalizations and comorbidities. Two sites are also not appropriate with the total amount of 30 000 euros available. Randomization of patients is also not possible in this study due to a high risk of contamination bias. Indeed, once the clinical pharmacist arrives in the care unit, he or she should change the medical apprehension for the PICC prescribers and nurses, explaining the good use and follow up of the PICC line, affecting all the future included patients, even the control group.

Furthermore, we wish to set up a larger, multicenter, randomized, stepped-wedge study. A randomization by cluster (participating centers) will then be carried out. Different periods of time (control and intervention) are foreseen for each investigation center. Our current study and its results will allow us to establish the feasibility of the multicenter project and to have preliminary answers to the question of the effectiveness of the clinical pharmacist for the prevention of certain complications due to the presence of implantable medical devices.

For these reasons, and to prepare the next study, we decided to be as close as possible to the process of the future stepped-wedge design in each center: before-after clinical pharmacy activities. We are aware though, that the current before-after design in a single center, without patients' randomization, is highly censurable.

Setting

We propose a monocentric study that will take place in the Toulouse University Hospital Center. Inclusions will take place in the interventional radiology unit where all the prescriptions for PICC line are received. For each phase, observational and interventional, 69 patients will be recruited (refer to "Sample Size Calculation"). By the end of the recruitment, 138 patients will be enrolled in the study. For each phase, it will take 6 months to obtain the necessary number of subjects. See Figure 1 for study timeline.

Characteristics of participants: Inclusion and exclusion criteria

All selected patients will give an informed and signed consent to participate. All adult patients in need of a PICC line and whose care project includes a return home implanted with it are eligible to inclusion (Table 1). The patients have to be reachable by phone too. For all included patients, we will calculate the Charlson's score(49) to assess a degree of comorbidity at baseline.

Inclusion criteria	Exclusion criteria
Adult patient, age equal to or older than 18 years old Patient capable of giving free and informed consent Patient insured by the Social Security System Patient living at home Patient with a PICC line prescription Patient whose discharge prescription should contain drugs and MDs Patient for home discharge implanted with a PICC line Patient reachable by phone	Under-aged patient, age under 18 years old Uninsured patient by the Social Security System Patient not living at home : Institutionalized patient Patient living in a home for elderly dependent persons Nursing home resident Home-hospitalized patient Patient deprived of liberty by a judicial or administrative decision Patient under guardianship, curatorship or safeguard of justice Patient unreachable by phone Pregnant or breastfeeding women

Table 1 : Inclusion and exclusion criteria

Process

The study will start with an observational period and will continue with the interventional phase. For each phase, we will track PICC line complications during hospitalization and by phone calls after discharge. The telephone follow-up will concern all implanted patient for a maximum of 3 months. Data will be collected at days 3 and 7 after implantation and then at 1, 2 and 3 months after.

The control period represents the observational phase or arm, where no pharmaceutic interventions will be done, unless it is necessary for the patient safety. The observational phase corresponds to usual cares. These data will be compared to the data collected in the other arm of the study: the interventional phase. The close telephone follow-up with nurses, physicians in primary care and patients themselves after discharge will give us valuable data on complications rates and use of care.

- During the observational phase, no information will be transmitted to the healthcare teams or the patients except for judged life-threatening situations.

- During the interventional phase, we will use the same scheme as the observational phase, but with pharmaceutical interventions and activities in every step of the way if necessary.

Two pharmacists, among them the investigator, and a pharmacy resident will participate in each phase. They will be in charge of the data collection and the follow-up calls in both phases, as well as deploying pharmaceutical care activities during the interventional phase. All stages described below, even phone calls, will be recorded in traceability forms using specific indicators or items, for harmonization of data collection.

Observational phase

For each included patient in the observational arm, many criteria will be recorded to create the database of the study:

During hospitalization:

- Analysis of the PICC line insertion indication in the medical record and in the order for the PICC line addressed to the operating room and in care service if necessary.
- In the operating room:
  - Verification of the availability of the equipment necessary for implementation.
  - Conformity assessment of the expiration date in all PICC lines stored in the operating room.
  - Conformity assessment of the traceability serial number from the pharmacy received order of the MDs to the delivery in the care unit.
- After implantation:
  - Conformity assessment of the traceability serial number in the patient record and handing over the leaflet of traceability with required information (date of

implantation, serial number, name of PICC line, industrial company name and physician).

- Recording of eventual complications in patient's file and in the care unit during hospitalization.

At discharge:

- Analysis of medicines and medical devices in the discharge prescription based on the patient's history and comorbidities. Recording of potentially inappropriate medications (PIM) according to the gold standard or START and STOPP method(50) or European PIM list(51) for older adults.

At home:

- The patient will be called twice the first seven days and then at one, two and 3 months (M1, M2 and M3 respectively) to collect eventual clinical data on complications or any events.
- The liberal nurse will be called at the same frequency to confirm or infirm the presence of complications and to record events related to patient care.
- The dispensary pharmacist will be called at M1, M2 and M3 to record all the information necessary for patient follow-up.
- The general practitioner will be called only if there is a need to confirm clinical data on complications such as thrombotic events or at the end of the follow-up to identify any consultations in connection with the PICC line and any other relevant information on the patient's follow-up.

Interventional phase

The interventional phase will start when the last patient of the observational phase is included and will implement many clinical pharmacy activities:

Trainings for hospital professionals

Intended for physicians and nurses, as well as other healthcare professionals, in the departments that prescribe the most of the PICC lines, updates on recommendations, indications and maintenance regarding the use of PICC lines will be proposed. This training will last 15 to 20 minutes and will be repeated once to make sure that we have met with all the professionals involved. A sign-in sheet will be completed for the traceability of the interventions.

Clinical pharmacy with the prescribers for each included patient

- Analysis of the PICC line insertion indication.
- Verification in relation to the patient's medical record and the information given by the prescriber:
    - Discussion with the prescriber to ensure that the indication and duration of insertion of the PICC line comply with good practice.
    - Pharmaceutical interventions are likely to be carried out in the event of unjustified deviation from the recommendations. They may concern the indication itself; the product(s) prescribed, the expected duration of insertion, the medical device chosen (one or two channels).

Clinical pharmacy with the health professional in operating room for each included patient

- Verification of the availability of the equipment necessary for implementation.
- Conformity assessment of the expiration date in all PICC lines stored in the operating room.
- Conformity assessment of the traceability serial number from the pharmacy received order to the delivery in the care unit.
- Conformity assessment of the traceability serial number in the patient record and the handing over of the traceability leaflet with required information (date of implantation, serial number, name of PICC line, industrial company name and physician)

Clinical pharmacy with nurses for each included patient

The clinical pharmacist will personally give a PICC line maintenance booklet to the patients' nurses and ensure that the professional consults it. The mainly principles of PICC line follow up will be explained orally twice during nurses' rotations, in order to be sure to meet all the professionals involved.

Clinical pharmacy for logistic topics in the operating room and economic costs:

- The number of medical devices used and thrown during the procedure.
- The presence or absence of non-functional devices (expired, broken, etc.).
- The traceability of the batch number of the medical device implanted in the operating room software within a period of 24 hours.

Clinical pharmacy at discharge

- Pharmaceutical analysis of the patient's discharge order in readiness for optimization if necessary.
- Pharmaceutical interventions:
    - The analysis will focus on drugs and MDs prescribed in connection with the PICC line (e.g. dressing repair set). The prescription will be optimized according to gold standard or as START and STOPP method(50) or European PIM list(51) for older adults.
- Pharmaceutical interview with the patient:
    - Assess the patient's knowledge and comprehension capacity.
    - Discuss the different treatments prescribed on the discharge order, explain them to the patient if necessary, answer any questions, and reassure the patient if necessary.
    - Provide clear information to the patient about the PICC line, the purpose of its utilization, how to maintain it and to detect eventual complications.
    - Make sure that the patient has received the traceability sheet of paper required for the return home or give it to him or her if necessary.
    - Make sure that the patient has received the PICC line user's booklet or give it to the patient if necessary.

- Allow the patient to summarize briefly the key points discussed during the interview to ensure optimal understanding.

- Assessment of the patient's quality of life using the validated EQ5D5L scale. A second version will be given to fill out the survey at the end of 3 months (control versus end of follow-up assessment).
- Call to the dispensary pharmacist to transmit the patient's prescription to him/her and allowing him or her to anticipate dispensing if necessary.

Clinical pharmacy during the follow-up in primary care

- The patient will be called twice the first seven days and then at M1, M2 and M3 to collect clinical data on complications or any events and give pharmaceutical advices if necessary and answer any questions.
- The liberal nurse will be called at the same frequency to confirm or infirm the presence of complications, record events related to patient care, give pharmaceutical advices if necessary and answer to any questions.
- The dispensary pharmacist will be recalled at M1, M2 and M3 to record all the information necessary for the patient's follow-up.
- The general practitioner will be called if there is a need to confirm clinical data on complications such as thrombotic events or at the end of the follow-up to identify any consultations in connection with the PICC line and any other relevant information on the patient's follow-up.

Satisfaction survey

At the end of the study, a satisfaction survey will be sent to every care providers involved in the therapeutic management and every patients. Return envelopes will be provided.

Figure 2 resumes each stage of the process.

Blinding

It is an open study and due to the nature of the pharmaceutical interventions, blinding is not possible for patients and care providers.

Comparison

We will compare the primary and secondary endpoints between the two arms of the study.

Outcomes and expected benefits

Primary outcome

It will assess the number of complications per patient and per month. It will be evaluated prospectively for each phase at days 3 and 7 and then at M1, M2 and M3 after discharge. The number of complications will be collected by specific interviews given to the patients and confirmed by interviews given to the patients' healthcare professionals (liberal nurses, dispensary pharmacists and general practitioner if necessary). We shall distinguish two types of complications, mechanical and clinical.

The mechanical complications are listed as follow: obstruction, break, migration, unintentional clamp or accidental withdrawal of the catheter.

The clinical complications are defined as redness around the insertion site (diameter >2cm), edema (size difference between the two hands), pain (pain numeric scale), fever (intern temperature >37°C) and thrombotic events. These last ones will be confirmed by a medical control (echography).

Secondary outcomes

- The number of consultations and rehospitalizations post-discharge is commonly used in trials to determine a clinical impact beyond the initial hospitalization(13,52–54). We want to measure the impact of clinical pharmacy interventions on the consultations and

hospitalizations rates. We will compare the two arms and we hope to show a significant diminution of these rates after the intervention period.

- The number of potentially inappropriate prescriptions according to gold standard for adults and older adults.
- The acceptance rate of pharmaceutical interventions during the interventional phase is also commonly used in several studies to assess the appropriateness of pharmaceutical interventions(55–59). The higher the acceptance rate is, the more we can assume that our interventions are justified and relevant to the care providers.
- Evaluation of the criticality of the pharmacists' interventions(60).
- The conformity analysis of the PICC line logistic circuit (items checklist about stock, supply chain, traceability). The management of the hospital supply chain is a major economic challenge and lead generally to a decreased care risk (61). We hope to streamline the various stages of the PICC lines logistic circuit, from ordering to implantation. The aim is to solve precisely the services' issues for a better stock management as well as to raise awareness about MD's traceability. By rationalizing the logistics, we believe we will have both an economic impact and an impact on improving patient safety.
- The conformity analysis of the treatment indication. We hypothesize that PICC lines prescription may be too often trivialized and little guided by attending doctors. We suppose that errors could exist regarding the indications of treatment as well as errors in the PICC lines logistic circuit. Most of the time, the indication of the PICC line is not known by the interventional radiology teams nor is the necessary implementation time. The aim is to recall or make known the different indications of a PICC line, the treatment durations if necessary, thus contributing to an improvement of practices.
- The conformity analysis of the hospital prescriptions issued in town. Ensuring the conformity of these prescriptions is a regulatory requirement that falls within the framework of the

Contract to Improve the Quality and Efficiency of Care (62,63) (an obligation under French law). The aim is to ensure that healthcare spending is kept under control.

- The patients' quality of life before and after the follow-up (EQD5DL Scale). Quality of life is only minimally assessed in studies evaluating clinical pharmacy and the results about a possible improvement are inconclusive and differ between studies (16,64,65). We believe that using a validated tool will allow us to obtain a robust result relating to the theoretical improvement of quality of life in patients in the interventional phase. In addition, we will compare patients' assessments at discharge with those at the end of follow-up.
- The satisfaction of the patients and the care providers involved. These evaluations allow us, on the one hand, to know the patients' point of view regarding their pharmaceutical management. On the other hand, they allow us to measure the satisfaction of the various healthcare professionals who work with us. To develop clinical pharmacy activities in health care services, collaboration and communication with health care teams is essential.
- The description and evaluation of the direct hospital costs. The calculation of direct hospital medical costs will allow us to estimate whether additional costs are induced, or whether if costs are spared through better organization and management of the logistics circuit.

Statistical analysis

Appropriate statistical tests according to the distribution of variables will be used. All tests will be performed at alpha risk = 5%. When necessary, a logistic regression on potential confounding factors will be considered.

Sample Size Calculation

According to the ENEIS studies (2004 and 2009) and their final report (66), at least 50% of iatrogenic serious adverse events are preventable whether it concerns the medicines field or MDs field.

We assume that our pharmaceutical interventions and the integration of clinical pharmacy practices will lead to a theoretical 25% decrease of the complication rate in the interventional phase. To achieve this 25% reduction (strength of 80% and alpha risk of 5%), 62 patients are needed in each group. We can imagine that 10% of the patients will be potentially lost to follow-up, thus the number of patients is expanded to 138 patients.

All early exits from the study will be considered as lost to follow-up and the affected data will be processed in the statistical analysis as intent-to-treat.

Descriptive statistics

Descriptive statistics will be used to describe the demographic and clinical characteristics of the patients. Categorical variables will be described by counts and percentages. Means and standard deviations will be reported for continuous variables with normal distribution, and median and quartiles for other continuous variables. The Charlson score will be used to compare the levels of comorbidity between the two groups (Student t-test) and ensure the groups' comparability.

The acceptance rate of pharmaceutical interventions during the interventional phase. The acceptance rate will be expressed as a percentage of accepted pharmaceutical interventions out of the total number of pharmaceutical interventions. The proportion of potentially inappropriate prescription will be assessed.

Statistic comparisons

Comparisons will be made with Student's t-test or the corresponding nonparametric test for quantitative variables. For qualitative variables, the Chi^2 test or the Fisher's exact test will be used.

The primary outcome is the number of complications per patient and per month. The means or medians corresponding to each phase will be assessed. To compare the means or medians of the number of complications per month and per patient between the two phases, we will use a Poisson model or negative binomial regression if we face an over-dispersion phenomenon. We consider using

an adjustment for confounding factors such as sex and age. The decrease in the complication rate in the interventional phase will be expressed as a percentage. This proportion will be compared to our theoretical rate of 25% using the Chi^2 test or the Fisher's exact test.

The secondary outcomes will be described as follows:

- The numbers of consultations and rehospitalizations post-discharge will be expressed as means or the medians corresponding to each phase. The numbers of consultations and rehospitalizations post-discharge. The comparison of the means or medians of the two groups will be made with the Student's t-test or the Wilcoxon's test.
- The conformity of the logistic circuit of PICC lines will be expressed in number of correct items out of the total number of items (checklist). The conformity rate for each phase will be expressed as a percentage.
- Indications of the implantation of the PICC lines will expressed in proportions. The comparisons within and between groups will be carried out using Chi2 or test. Conformity rates for indications in both groups will be expressed as percentages.

Comparisons of the proportions for the two precedent objectives will be carried out using a Chi^2 test or an exact Fisher test.

- The conformity analysis of the hospital prescriptions issued in town. The conformity rate of hospital prescriptions executed in the city will be expressed in proportions for both phases. The proportions of each of the phases will be compared using adapted tests (Chi^2 or Fisher's exact test).
- As for the patients' quality of life before and after the follow-up (EQD5DL Scale), means or medians corresponding to each group will be assessed. Comparison of quality of life assessments at discharge and at the end of follow-up will be done using a Student's test or a Wilcoxon's test as well as comparison between groups.

- Participants will be sorted according to their level of satisfaction after the satisfaction survey. Satisfactions levels will be expressed in proportions, therefore Chi^2 or Fisher's exact tests will be used for comparisons.
- Direct intra-hospital medical costs will be calculated for each phase. These costs will be expressed as an average cost per patient. The difference in cost between the two phases will be analyzed using tests adapted to quantitative variables.

Discussion

The main objective is to demonstrate the effectiveness of clinical pharmacy in the prevention of complications in patients implanted with a PICC line. The literature is very rich regarding the occurrence of complications following the insertion of a PICC line, in hospital(30–38) or at home(39–45). At the same time, reported rates vary widely across studies. We therefore had to pool these rates of occurrence to estimate an "average" rate of occurrence of complications. This method allowed us to calculate the number of subjects necessary to observe a theoretical 25% decrease in the complication rate during the interventional phase. These assumptions have an impact on the robustness of our study and could lead to the use of statistical adjustments when analyzing the results. The numbers of consultations and rehospitalizations post-discharge are commonly used in several studies, particularly the 30-day readmission rate (13,54,67–69) to assess clinical effectiveness of pharmacists interventions. In order to be able to compare with existing studies, we thought these rates were relevant for analysis even if results are very heterogeneous in literature. However, it will be difficult to obtain exhaustive results, as the data will be provided by the declarations of the different actors. The information will only be formally verifiable if the patient concerned is readmitted or consults in one of the departments of our establishment.

Regarding the acceptance rate of pharmaceutical interventions during the interventional phase, pharmacists in charge will trace all the pharmaceutical interventions. The acceptance rate is not only a widely used and recognized means of assessing the appropriateness of interventions, it is also an

indicator routinely used in hospitals. We should not have any particular difficulty in calculating this acceptance rate.

We have developed a checklist of items in order to evaluate the conformity of the PICC line logistic circuit. This list is particularly exhaustive and will be used by all actors in charge of collecting the data. Therefore we avoid both an evaluation bias that could be linked to the multiplicity of actors involved, as well as a possible differential bias that could be linked to the different experience of operators. We should have no difficulty in establishing the compliance rates in both groups. The checklist will allow us to identify the most common errors or pitfalls encountered and to establish adequate corrective measures.

As for the conformity of the circuit, an exhaustive checklist has been developed based on current guidelines. We should not encounter any particular difficulty in assessing the conformity of the indication with good practice and recommendations and with the patient's medical record to which all pharmacists involved have access.

The conformity analysis of the hospital prescriptions issued in town is part of secondary endpoints. In compliance with the law, it seems essential to us to propose a way to be systematic in the analysis of these prescriptions.

Assessments of patients' quality of life before and after the follow-up using the EQ-5D-5L Scale are possible because of the prospective methodology. This criterion is relevant to assess the point of view of the patient, the central actor in the care pathway. In order to avoid as much interference or influence as possible due to our presence, we will propose not to be present at the time of the first evaluation (the day of discharge). However, the following assessments will be done by telephone and we may influence patient responses.

Likert's scales have been developed to collect patient and healthcare professional satisfaction data. These tools are validated and reliable for collecting the opinions of different research participants. These scales allow obtaining more nuanced opinions, better understanding the feedback and identifying areas for improvement. The different parties generally appreciate these tools and we

should not encounter any particular difficulties in both collecting and analyzing these results. Nevertheless, patients will not be the same between the observational and interventional phases. Consequently, the differences observed regarding satisfaction, if any, may also be due to difference of individuals between the two groups. A low response rate from professionals to the satisfaction survey is to be expected, as described in the literature.

The measurement and analysis of costs is limited to direct hospital medical costs, which does not allow an overall analysis of the costs of care. As the primary objective is a clinical endpoint, we reserve further medico-economic analysis for a multicenter study.

This study concerns only one hospital with a focus on one medical device. It is only the preliminary stage for scaling up a larger, multi-center and randomized trial with several implantable medical devices (IMDs). The future study will follow a stepped-wedge method consisting of randomization by center and not by patient for the deployment of before-and-after phases in each of the participating centers.

Our study therefore represents the step towards obtaining efficacy results on clinical pharmacy applied to IMDs with the aim of a larger-scale study with a more rigorous methodology.

This is the first step towards a change in practices, an improved communication between professionals, a better collaboration and the integration of the clinical pharmacist into the multidisciplinary team.

We do not pretend to show any methodological or statistical prowess but the suggested before-after design appears to be the closest to the stepped-wedge method since they share separate observational and interventional periods. Indeed, randomization is not possible given the nature of the intervention and the high risk of contamination bias. We are fully aware of this highly critical point.

This trial will investigate the impact of the integration of clinical pharmacy activities during the global care pathway of patients implanted with a PICC line on preventing post-procedural complications. This study is the first, to our knowledge, to focus on clinical pharmacy applied to implantable medical devices with a hard clinical endpoint as its main objective.

Potential limitations and bias

Since the study is not randomized, we are subject to selection bias and risk two non-comparable samples. To overcome this limitation, we plan to compare the two groups using a Poisson model or a negative binomial regression (in case of over-dispersion). In addition, an adjustment on the main confounding factors (such as age, sex and comorbidity index) will be considered.

Blinding is not possible due to the nature of the intervention. There is a risk of measurement bias for patients in the interventional phase as well as for pharmacists who record the number of complications per patient because of the subjectivity of each. We hope to limit this risk by having the primary endpoint analyzed by a blind methodologist. Measurement bias is almost inevitable when assessing the quality of life of patients in the interventional phase as explained above.

Recruitment may be longer than expected because all the PICC lines are placed in the operating room and are not a priority as opposed to vital emergencies.

Phone calls to collect clinical data on complications, deaths and rehospitalizations are limited. They will remain on the patients' and care providers' statements. It is possible that some omit intentionally or unintentionally to communicate some information. The plurality of involved counterparts may help to corroborate the given information. We plan to harmonize data collection by double-checking the collection forms and the information collected at the time of pharmaceutical interviews and calls.

Trial status

National registration number: 2019-A02475-52

On *Clinical Trials*: Not yet applicable.

Abbreviations

ENEIS: Enquête nationale sur les évènements indésirables graves associés aux soins (national inquiry on iatrogenic serious adverse events). HAS: Haute Autorité de Santé (High Health Autority).

Authors' statement

Alix Marie POUGET, Elodie CIVADE and Charlotte ROUZAUD-LABORDE contributed to the conception of the study. The authors will be in charge of the acquisition and analysis of the data, interpretation and diffusion of the results.

Alix Marie POUGET and Charlotte ROUZAUD-LABORDE contributed to the draft.

All four authors contributed to the revision of the work and gave their final approval of the version to be published.

All authors have agreed to be accountable for all aspects of the study such as accuracy and integrity of the work.

Author's declarations

There is no personal data in the protocol.

Additional data and materials are not available except through the corresponding author.

The authors do not declare any conflict of interest.

Sponsor

The Research and Innovation Board of the Toulouse University Hospital Center is the promoter of this study. The protocol is locally registered with the following number: RC31/18/0459.

Funding

This work is supported by a grant from the Foundation for Hospital Pharmacy Research and the French Society of Clinical Pharmacy (Call for Projects, November 2018).

Ethics and dissemination

An independent protection committee (South-East VI, Clermont-Ferrand, France) assessed the scientific ethic of the protocol (version dated 3 February 2020) and authorized this trial.

All data collected will be anonymized and access to the data will be restricted to those participating in the research (investigators, pharmacists and pharmacy residents).

The results of the study will be published when available.

Acknowledgements

The authors thank the Foundation for Hospital Research and the French Society of Clinical Pharmacy for choosing this project to be developed and the financial help provided.

References

1. Société Française de Pharmacie Clinique (SFPC). Présentation de la Pharmacie Clinique [Internet]. 2016. Available from: http://sfpc.eu/fr/la-sfpc/presentation.html

2. Allenet B, Juste M, Mouchoux C, Collomp R, Pourrat X, Varin R, et al. De la dispensation au plan pharmaceutique personnalisé : vers un modèle intégratif de pharmacie clinique. Le Pharm Hosp Clin. 2019;54(1):56–63.

3. Ordonnance n° 2016-1729 du 15 décembre 2016 relative aux pharmacies à usage intérieur. J Off la République Française. 2016;0292(32).

4. Code de la santé publique - Article R5126-10 | Legifrance [Internet]. [cited 2019 Dec 4]. Available from: https://www.legifrance.gouv.fr/affichCodeArticle.do?idArticle=LEGIARTI000038598051&cidTexte=LEGITEXT000006072665&dateTexte=20190524

5. Arrêté du 31 juillet 2019 définissant les orientations pluriannuelles prioritaires de développement professionnel continu pour les années 2020 à 2022 | Legifrance [Internet]. [cited 2019 Dec 4]. Available from: https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000038858372&categorieLien=id

6. Jack BW, Chetty VK, Anthony D, Greenwald JL, Sanchez GM, Johnson AE, et al. A Reengineered Hospital Discharge Program to Decrease Rehospitalization: A Randomized Trial [Internet]. 2009 [cited 2019 Dec 2]. Available from: www.annals.org.

7. Pal A, Babbott S, Wilkinson ST. Can the targeted use of a discharge pharmacist significantly decrease 30-day readmissions? Hosp Pharm. 2013 May 1;48(5):380–8.

8. McKay C, Park C, Chang J, Brackbill M, Choi JY, Lee JH, et al. Systematic Review and Meta-analysis of Pharmacist-Led Transitions of Care Services on the 30-Day All-Cause Readmission

Rate of Patients with Congestive Heart Failure. Vol. 39, Clinical Drug Investigation. Springer International Publishing; 2019. p. 703–12.

9. Renaudin P, Boyer L, Esteve M-A, Bertault-Peres P, Auquier P, Honore S. Do pharmacist-led medication reviews in hospitals help reduce hospital readmissions? A systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82(6):1660–73.

10. Haute Autorité de Santé - Mettre en œuvre la conciliation des traitements médicamenteux en établissement de santé [Internet]. [cited 2019 Dec 2]. Available from: https://www.has-sante.fr/jcms/c_2736453/fr/mettre-en-oeuvre-la-conciliation-des-traitements-medicamenteux-en-etablissement-de-sante

11. Leguelinel-Blache G, Arnaud F, Bouvet S, Dubois F, Castelli C, Roux-Marson C, et al. Impact of admission medication reconciliation performed by clinical pharmacists on medication safety. Eur J Intern Med [Internet]. 2014;25(9):808–14. Available from: http://dx.doi.org/10.1016/j.ejim.2014.09.012

12. Lehnbom EC, Stewart MJ, Manias E, Westbrook JI. Impact of Medication Reconciliation and Review on Clinical Outcomes. Ann Pharmacother. 2014;48(10):1298–312.

13. Mekonnen AB, McLachlan AJ, Brien JAE. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: A systematic review and meta-analysis. Vol. 6, BMJ Open. BMJ Publishing Group; 2016.

14. Daliri S, Hugtenburg JG, Ter Riet G, Van den Bemt BJF, Buurman BM, Scholte op Reimer WJM, et al. The effect of a pharmacy-led transitional care program on medication-related problems post-discharge: A before—After prospective study. PLoS One. 2019 Mar 1;14(3).

15. Lipton HL, Bird JA. The Impact of Clinical Pharmacists' Consultations on Geriatric Patients' Compliance and Medical Care Use: A Randomized Controlled Trial. Gerontologist. 2011;34(3):307–15.

16. Sadik A, Yousif M, McElnay JC. Pharmaceutical care of patients with heart failure. Br J Clin Pharmacol. 2005;60(2):183–93.

17. Ferrand E, Painchart L, Grimandi G, Décaudin B, Bussières J. Rôles et retombées des pharmaciens dans la gestion des dispositifs médicaux en établissement de santé : une revue de littérature. Ann Pharm Fr [Internet]. 2017; Available from: http://dx.doi.org/10.1016/j.pharma.2017.05.001

18. Roussel C, Carbonneil C, Audry A, Burtey S, Faré S, Langevin F, et al. Impact organisationnel : définition et méthodes d'évaluation pour les dispositifs médicaux. Therapie. 2016;71(1):69–82.

19. Painchart L, Drancourt P, Aubert J, Inghels Y, Boyer J. Interest and difficulties in setting up pharmaceutical reconciliations for patients with dressings for complex wounds. Ann Pharm Fr. 2019;

20. Skjøt-Arkil H, Lundby C, Kjeldsen LJ, Skovgårds DM, Almarsdóttir AB, Kjølhede T, et al. Multifaceted Pharmacist-led Interventions in the Hospital Setting: A Systematic Review. Vol. 123, Basic and Clinical Pharmacology and Toxicology. Blackwell Publishing Ltd; 2018. p. 363–79.

21. Gonçalves-Bradley DC, Lannin NA, Clemson LM, Cameron ID, Shepperd S. Discharge planning from hospital. Vol. 2016, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2016.

22. Epstein N. Multidisciplinary in-hospital teams improve patient outcomes: A review. Surg Neurol Int. 2014;5(8):295.

23. Meyer-Massetti C, Hofstetter V, Hedinger-Grogg B, Meier CR, Guglielmo BJ. Medication-related problems during transfer from hospital to home care: baseline data from Switzerland. Int J Clin Pharm. 2018;

24. Hirschman KB, Shaid E, McCauley K, Pauly M V., Naylor MD. Continuity of care: The transitional care mode. Online J Issues Nurs. 2015;20(3).

25. Bonaudo M, Martorana M, Dimonte V, D'Alfonso A, Fornero G, Politano G, et al. Medication discrepancies across multiple care transitions: A retrospective longitudinal cohort study in Italy. PLoS One. 2018;13(1).

26. Kripalani S, LeFevre F, Phillips CO, Williams M V., Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: Implications for patient safety and continuity of care. Vol. 297, Journal of the American Medical Association. American Medical Association; 2007. p. 831–41.

27. Kwan JL, Lo L, Sampson M, Shojania KG. Medication reconciliation during transitions of care as a patient safety strategy: A systematic review. Vol. 158, Annals of Internal Medicine. American College of Physicians; 2013. p. 397–403.

28. Kumar A, Kethireddy S, Darovic GO. Catheter-related and infusion-related sepsis. Vol. 29, Critical Care Clinics. Crit Care Clin; 2013. p. 989–1015.

29. Rupp ME, Karnatak R. Intravascular Catheter–Related Bloodstream Infections. Vol. 32, Infectious Disease Clinics of North America. W.B. Saunders; 2018. p. 765–87.

30. Grove JR, Pevec WC. Venous thrombosis related to peripherally inserted central catheters. J Vasc Interv Radiol. 2000;11(7):837–40.

31. Cowl CT, Weinstock J V., Al-Jurf A, Ephgrave K, Murray JA, Dillon K. Complications and cost associated with parenteral nutrition delivered to hospitalized patients through either subclavian or peripherally-inserted central catheters. Clin Nutr. 2000;19(4):237–43.

32. Vidal V, Muller C, Jacquier A, Giorgi R, Le Corroller T, Gaubert JY, et al. Évaluation prospective des complications des PICCs. J Radiol [Internet]. 2008;89(4):495–8. Available from: http://dx.doi.org/10.1016/S0221-0363(08)71453-7

33. Amerasekera SSH, Jones CM, Patel R, Cleasby MJ. Imaging of the complications of peripherally inserted central venous catheters. Clin Radiol [Internet]. 2009;64(8):832–40. Available from:

http://dx.doi.org/10.1016/j.crad.2009.02.021

34. Leroyer C, Lashéras A, Marie V, Le Bras Y, Carteret T, Dupon M, et al. Prospective follow-up of complications related to peripherally inserted central catheters. Med Mal Infect [Internet]. 2013;43(8):350–5. Available from: http://dx.doi.org/10.1016/j.medmal.2013.06.013

35. Greene MT, Flanders SA, Woller SC, Bernstein SJ, Chopra V. The Association between PICC Use and Venous Thromboembolism in Upper and Lower Extremities. Am J Med. 2015;128(9).

36. Fallouh N, McGuirk HM, Flanders SA, Chopra V. Peripherally inserted central catheter-associated deep vein thrombosis: A narrative review. Am J Med. 2015;128(7).

37. Bertoglio S, Faccini B, Lalli L, Cafiero F, Bruzzi P. Peripherally inserted central catheters (PICCs) in cancer patients under chemotherapy: A prospective study on the incidence of complications and overall failures. J Surg Oncol. 2016;113(6).

38. Jones D, Wismayer K, Bozas G, Palmer J, Elliott M, Maraveyas A. The risk of venous thromboembolism associated with peripherally inserted central catheters in ambulant cancer patients. Thromb J. 2017;15(1):1–6.

39. Dreesen M, Foulon V, Spriet I, Goossens GA, Hiele M, De Pourcq L, et al. Epidemiology of catheter-related infections in adult patients receiving home parenteral nutrition: A systematic review. Clin Nutr [Internet]. 2013;32(1):16–26. Available from: http://dx.doi.org/10.1016/j.clnu.2012.08.004

40. Touré A, Duchamp A, Peraldi C, Barnoud D, Lauverjat M, Gelas P, et al. A comparative study of peripherally-inserted and Broviac catheter complications in home parenteral nutrition patients. Clin Nutr [Internet]. 2015;34(1):49–52. Available from: http://dx.doi.org/10.1016/j.clnu.2013.12.017

41. Christensen LD, Holst M, Bech LF, Drustrup L, Nygaard L, Skallerup A, et al. Comparison of complications associated with peripherally inserted central catheters and Hickman™ catheters

in patients with intestinal failure receiving home parenteral nutrition. Six-year follow up study. Clin Nutr [Internet]. 2016;35(4):912–7. Available from: http://dx.doi.org/10.1016/j.clnu.2015.06.009

42. Ross VM, Guenter P, Corrigan ML, Kovacevich D, Winkler MF, Resnick HE, et al. Central venous catheter infections in home parenteral nutrition patients: Outcomes from Sustain: American Society for Parenteral and Enteral Nutrition's National Patient Registry for Nutrition Care. Am J Infect Control [Internet]. 2016;44(12):1462–8. Available from: http://dx.doi.org/10.1016/j.ajic.2016.06.028

43. Grau D, Clarivet B, Lotthé A, Bommart S, Parer S. Complications with peripherally inserted central catheters (PICCs) used in hospitalized patients and outpatients: A prospective cohort study. Antimicrob Resist Infect Control [Internet]. 2017;6(1):1–8. Available from: http://dx.doi.org/10.1186/s13756-016-0161-0

44. Opilla M. Peripherally Inserted Central Catheter Experience in Long-Term Home Parenteral Nutrition Patients. JAVA - J Assoc Vasc Access [Internet]. 2017;22(1):42–5. Available from: http://dx.doi.org/10.1016/j.java.2016.12.001

45. Santacruz E, Mateo-Lobo R, Riveiro J, Nattero L, Vega-Piñero B, Lomba G, et al. Infectious complications in home parenteral nutrition: A long-term study with peripherally inserted central catheters, tunneled catheters, and ports. Nutrition. 2019;58:89–93.

46. Europharmat. Tracabilité des dispositifs médicaux. Vol. 53. 2016.

47. Société Française d'Hygiène Hospitalière (SF2H). Bonnes Pratiques Et Gestion Des Risques Associés Au Picc -Hygiènes -Volume Xxi -N° 6. 2013; Available from: https://sf2h.net/wp-content/uploads/2014/05/SF2H_bonnes-pratiques-et-gestion-des-risques-associes-au-PICC-2013.pdf

48. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: Defining standard protocol items for clinical trials. Vol. 158, Annals of Internal

Medicine. American College of Physicians; 2013. p. 200–7.

49. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;

50. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72–83.

51. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol [Internet]. 2015 Jul 14 [cited 2020 Feb 24];71(7):861–75. Available from: http://link.springer.com/10.1007/s00228-015-1860-9

52. Unplanned hospital visits [Internet]. [cited 2019 Dec 23]. Available from: https://www.medicare.gov/hospitalcompare/Data/Hospital-returns.html

53. Koehler BE, Richter KM, Youngblood L, Cohen BA, Prengler ID, Cheng D, et al. Reduction of 30-day postdischarge hospital readmission or emergency department (ED) visit rates in high-risk elderly medical patients through delivery of a targeted care bundle. J Hosp Med. 2009;4(4):211–8.

54. Hohl CM, Partovi N, Ghement I, Wickham ME, McGrail K, Reddekopp LN, et al. Impact of early in-hospital medication review by clinical pharmacists on health services utilization. PLoS One. 2017;12(2):1–13.

55. Bedouch P, Charpiat B, Conort O, Rose FX, Escofier L, Juste M, et al. Assessment of clinical pharmacists' interventions in French Hospitals: Results of a multicenter study. Ann Pharmacother. 2008 Jul;42(7–8):1095–103.

56. Charpiat B, Bedouch P, Conort O, Rose FX, Juste M, Roubille R, et al. Opportunités d'erreurs médicamenteuses et interventions pharmaceutiques dans le cadre de la prescription

informatisée : Revue des données publiées par les pharmaciens hospitaliers français. Vol. 70, Annales Pharmaceutiques Francaises. 2012. p. 62–74.

57. Charpiat B, Conort O, Juste M, Rose FX, Roubille R, Bedouch P, et al. Mise à disposition de l'outil de codification des interventions pharmaceutiques de la Société française de pharmacie clinique : bilan à 10 ans et perspectives. Vol. 50, Pharmacien Hospitalier et Clinicien. Elsevier Masson SAS; 2015. p. e15–24.

58. Mongaret C, Quillet P, Vo TH, Aubert L, Fourgeaud M, Michelet-Huot E, et al. Predictive factors for clinically significant pharmacist interventions at hospital admission. Vol. 97, Medicine (United States). Lippincott Williams and Wilkins; 2018.

59. Aguiar K da S, Santos JM Dos, Cambrussi MC, Picolotto S, Carneiro MB. Patient safety and the value of pharmaceutical intervention in a cancer hospital. Einstein (Sao Paulo). 2018;16(1):eAO4122.

60. Ha Vo T. Evaluation of the potential impact of pharmacist interventions : development and validation of the CLEO multidimensional tool [Internet]. [cited 2020 Feb 24]. Available from: https://tel.archives-ouvertes.fr/tel-01315619

61. Chasseigne V, Leguelinel-Blache G, Nguyen TL, de Tayrac R, Prudhomme M, Kinowski JM, et al. Assessing the costs of disposable and reusable supplies wasted during surgeries. Int J Surg [Internet]. 2018;53:18–23. Available from: https://doi.org/10.1016/j.ijsu.2018.02.004

62. Légifrance - Publications officielles - Journal officiel - Arrêté du 27 avril 2017 relatif au contrat type d'amélioration de la qualité et de l'efficience des soins mentionné à l'article L. 162-30-2 du code de la sécurité sociale [Internet]. [cited 2020 Jan 29]. Available from: https://beta.legifrance.gouv.fr/jorf/id/JORFTEXT000034517810

63. Direction de la sécurité sociale, Sous-direction du financement du système de soins, Bureau des établissements de santé médico-sociaux. Instruction interministerielle N°DSS/A1/CNAMTS/2017/234 du 26 juillet 2017 relative à la mise en oeuvre du Contrat

d'Amélioration de la Qualité et de l'Efficience des Soins.

64. Pillay B, Wootten AC, Crowe H, Corcoran N, Tran B, Bowden P, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. Cancer Treat Rev [Internet]. 2016;42:56–72. Available from: http://dx.doi.org/10.1016/j.ctrv.2015.11.007

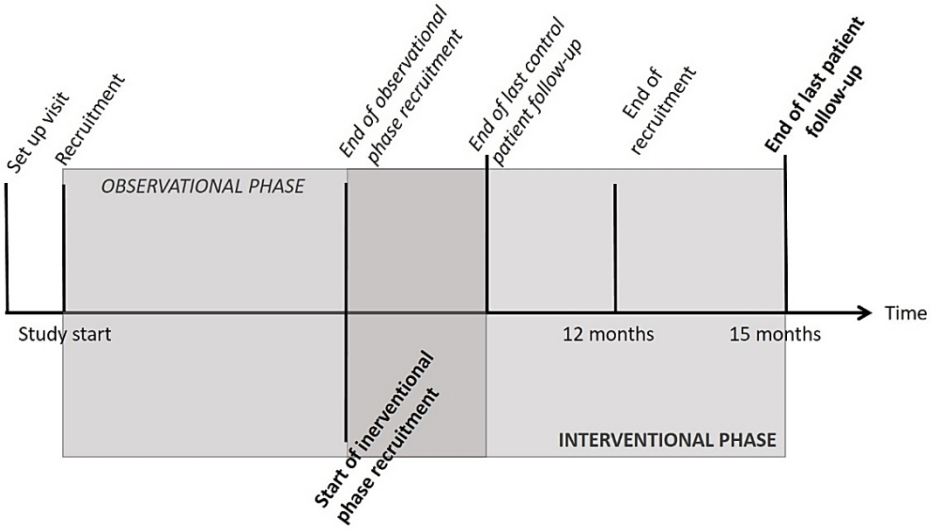
65. Beney J, Bero LA, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. Cochrane database Syst Rev [Internet]. 2000 [cited 2019 Dec 4];(3):CD000336. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10908471

66. Michel P, Lathelize M, Bru-Sonnet R, Perez C, Domecq S, Kret M, et al. Rapport final - Comparaison des deux études ENEIS 2004 et 2009. Drees, Ministère la santé. 2011;1–118.

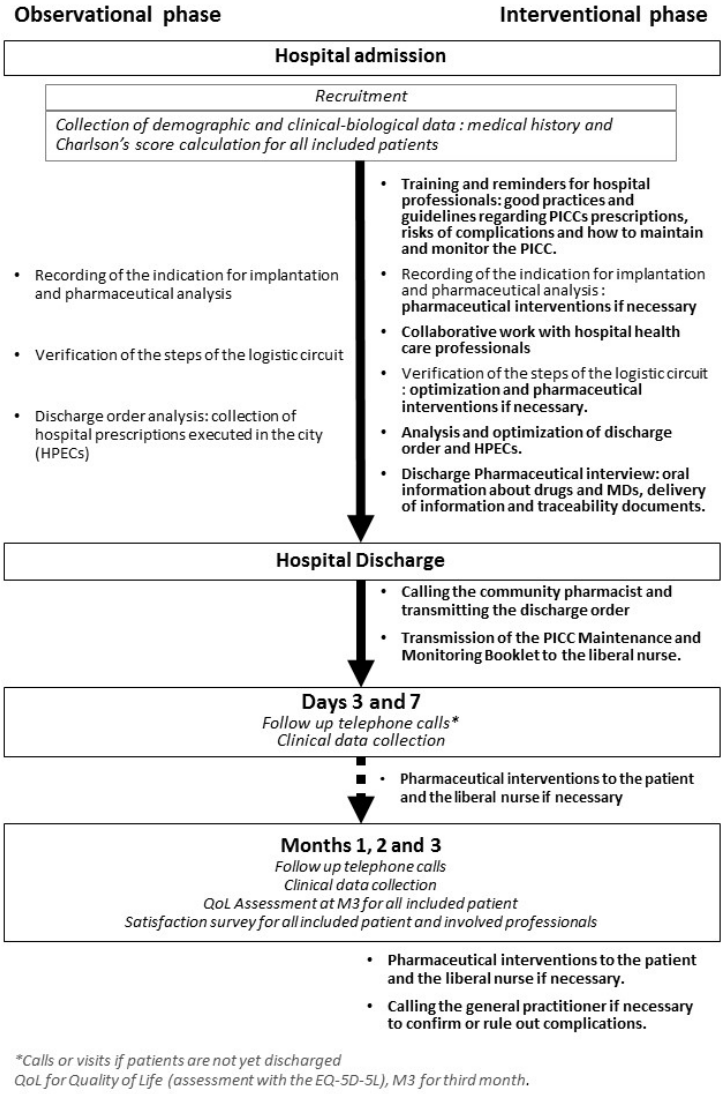
67. Kilcup M, Schultz D, Carlson J, Wilson B. Postdischarge pharmacist medication reconciliation: Impact on readmission rates and financial savings. J Am Pharm Assoc. 2013;53(1):78–84.

68. Jones CD, Anthony A, Klein MD, Shakowski C, Smith HK, Go A, et al. The effect of a pharmacist-led multidisciplinary transitions-of-care pilot for patients at high risk of readmission. J Am Pharm Assoc. 2018 Sep 1;58(5):554–60.

69. Lussier ME, Evans HJ, Wright EA, Gionfriddo MR. The impact of community pharmacist involvement on transitions of care: A systematic review and meta-analysis. J Am Pharm Assoc [Internet]. 2019; Available from: https://doi.org/10.1016/j.japh.2019.07.002



Study expected duration and setting. Each recruitment phase will last approximatively 6 months.



Summary of the different stages of the research - *Calls or visits if patients are not discharged yet – QoL for Quality of Life, M3 for third month of follow-up.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 23
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	24
Protocol version	#3	Date and version identifier	24
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	24
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	24
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data	24

		management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 4, 5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3, 4, 5
Objectives	#7	Specific objectives or hypotheses	4, 5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5, 6
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6, 7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9, 10, 11, 12
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, 9-12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	23
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	blinding is not possible in this study exept for analysis

Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	23

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods:			
Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	before-after study: interim analysis not necessary

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8-12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	24
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A, no ancillary studies planned

Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	24
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A , no ancillary trials.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	24

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24, all supplementary data through corresponding author
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	documents approuved by the ethic committee (24)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A, no biological specimens

Notes:

- 11a: 8, 9, 10, 11, 12
- 17b: blinding is not possible in this study exept for analysis
- 21b: before-after study: interim analysis not necessary
- 26b: N/A, no ancillary studies planned
- 30: N/A , no ancillary trials.
- 31c: 24, all supplementary data through corresponding author
- 32: documents approuved by the ethic committee (24)

- 33: N/A, no biological specimens This checklist was completed on 07. April 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

From hospitalization to primary care, integrative model of clinical pharmacy with patients implanted with a PICC line: research protocol for a prospective before-after study.

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From hospitalization to primary care, integrative model of clinical pharmacy with patients implanted with a PICC line: research protocol for a prospective before-after study

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Trial acronym: CLIPICC

Abstract

Introduction

Clinical pharmacy improves patient safety and secures drug management using information, education and good clinical practices. However, medical device management is still unexplored, and proof of effectiveness is needed. A PICC line is a medical device for infusion. It accesses the central venous system after being implanted in a peripheral vein. But complications after implantation often interfere with smooth execution of the treatment. We hypothesize that clinical pharmacy for medical devices could be as effective as clinical pharmacy for medications. The main objective is to assess the effectiveness of clinical pharmacy activities on the complication rate after PICC line implantation.

Methods and analysis

This is a before-after prospective study. The study will begin with an observational period without clinical pharmacy activities, followed by an interventional period where pharmacists will intervene on drug and medical device management and provide personalized follow-up and advice. Sixty-nine adult patients will be recruited in each 6-month period from all traditional care units. The main inclusion criteria will be the implantation of a PICC line. The primary outcome is the decrease in the number of complications per patient and per month. Secondary outcomes are the consultation and hospital readmission rates, the acceptance rate of pharmaceutical interventions, the patients' quality of life, the direct hospital induced or avoided costs and the participants' satisfaction. Data will be collected using Case Report Forms during hospitalization and telephone follow-up after discharge. The analysis will compare these criteria during the two periods.

Ethics and dissemination

The study has received the approval of our Ethics Committee (Clermont-Ferrand Southeast VI, France, number AU1586). Results will be made available to the patients or their caregivers, the sponsor and other researchers when asked, as described in the consent form.

Trial registration

2019-A02475-52 (ID-RCB number)
ClinicalTrials.gov*:* NCT04359056

Keywords

Clinical Pharmacy, Medical Devices, PICC lines, Protocol, Before-After Study

Strengths and Limitations

- This is the first study to assess the effectiveness of clinical pharmacy interventions for medical devices. The literature essentially works with medications, when medical devices are explored with pharmacist's activities; the patient impact is not evaluated.

- Strong clinical criteria will be evaluated by measuring skin redness, edema, thrombosis and pain. Our study does not measure intermediate criteria as a primary objective, such as the number of potentially inappropriate prescriptions.

- This study proposes an integrative model of clinical pharmacy, from hospitalization to primary care.

- The main limitations of this study are the lack of randomization and the lack of blinding for patients and healthcare professionals.

Introduction

Clinical pharmacy is a patient-centered health discipline whose practice aims to optimize therapy at each stage of the care pathway. Clinical pharmacy actions contribute to patient safety and the relevant and efficient use of health products (1). To ensure health products are used in a safe and appropriate manner, pharmacists analyze physicians' orders to identify errors or potentially inappropriate prescriptions based on guidelines and evidence-based medicine. Moreover, they optimize drug intake, inform patients and caregivers, organize the discharge to primary care and disseminate clinical good practices. Pharmacists also focus on patient education, information, and training for healthcare professionals.

Regarding medication approaches, the effectiveness of clinical pharmacy is well known. Several clinical studies have demonstrated significant impacts on re-hospitalizations (2–5), drug management (6) and treatment compliance (7), patients' quality of life(8) as well as a decrease of iatrogenic risk (9–12). But studies on clinical pharmacy in the context of medical devices (MD) are rare (13). To our knowledge, no study has described the clinical impact of a pharmacist's intervention when a MD is implanted in patients. Only one recent article refers to clinical pharmacy in dressings for complex wounds (14). The need for further clinical studies is undeniable.

MD classification is based on their risk of invasiveness and duration of use. Infusion equipment, such as catheters, can induce iatrogenic events, especially infections (15,16). Peripherally inserted central catheters (PICC lines) are associated with numerous clinical (e.g. infections (17)) and mechanical complications (e. g. catheter occlusions (18)) (19–27). PICC lines are useful for the administration of irritating products or for the repeated collection of blood samples. PICC lines are recommended when the duration of catheterization ranges from 7 days to 3 months (28). PICC line implantations are carried out in the interventional radiology operating room.

Our working hypothesis is that clinical pharmacy interventions will prevent clinical and mechanical complications and thereby reduce hospital costs(29). Reducing complications could also prevent its consequences such as rehospitalizations (30) and physician visits.

Methods and Analysis

A scientific committee (selected by the Research and Innovation Board of the Toulouse University Hospital) composed of scientific and methodological experts and statisticians oversaw the feasibility and methodology of the study. This committee ensures the quality and relevance of the research organization. The study procedures and assessments comply with the Standard Protocol Items: Recommendations for Interventional Trials (31).

Design

A pragmatic single center design is used. This is a before-after prospective study with two consecutive phases: observational (no clinical pharmacy activities) and interventional (execution of clinical pharmacy activities and logistics optimization). Randomization of patients is not possible in this study due to the high risk of contamination bias. Once the clinical pharmacist arrives in the care unit, he or she should address any medical apprehension by the PICC prescribers and nurses, explaining good clinical use, affecting all the future study patients, even the control group. This is an open study. Due to the nature of the pharmaceutical interventions, blinding is not possible for patients and care providers.

Setting

The study will take place in the Toulouse University Hospital Center. Every PICC line prescription will be picked up in the interventional radiology unit and patients will be screened for eligibility. Patients will be recruited from their hospital ward prior to the PICC line insertion. All selected participants will be asked to read and sign a consent form. Each phase (observational and interventional) will last

approximately 9 months taking into account recruitment and patient follow-up. See Figure 1 for the study timeline.

Recruitment began on Monday, May 25, 2020 and will end 1 year later on May 25, 2021. The study is scheduled to end on August 25, 2021.

Characteristics of participants: Inclusion and exclusion criteria

Eligibility criteria are listed in Table 1. For all included patients, the Charlson Comorbidity Index (32) will be use to assess the degree of comorbidity at baseline.

Inclusion criteria	Adult patient, 18 years of age or older Patient capable of giving free and informed consent Patient insured by the Social Security System in France Patient living at home Patient with a PICC line prescription Patient whose discharge prescription should contain drugs and MDs Patient for home discharge implanted with a PICC line Patient reachable by phone
Exclusion criteria	Under-aged patient, less than 18 years old Patient not insurance by the Social Security System in France Patient not living at home: Institutionalized patient Patient living in a facility for elderly dependent persons Nursing home resident “Hospital at Home” patient Patient deprived of their freedom by a judicial or administrative decision Patient under guardianship, curatorship or safeguard of justice Patient unreachable by phone Pregnant or breastfeeding women

Table 1 : Inclusion and exclusion criteria

Patient and public involvement

No patient involved.

Process

Regardless of the phase of the study, the occurrence of complications due to the PICC line will be recorded during hospitalization and at home during a follow-up phone call. Patients are monitored for the entire duration of the PICC line implantation or for a maximum of 3 months. Data will be collected at days 3 and 7 (D3 or D7 respectively) after implantation and then after 1, 2 and 3 months (M1, M2 and M3 respectively).

The control period corresponds to usual care and represents the observational phase, where no pharmaceutic interventions will be done, unless necessary for the patient's safety (e.g. life-threatening situations(33)).

One participant can be included in only one phase. The interventional phase will start when the last patient is included in the observational phase. Physicians and nurses, as well as other healthcare professionals, will attend training sessions on updates, recommendations, indications, and maintenance related the use of PICC lines. If necessary, training sessions will be repeated once to make sure the research team met all the healthcare professionals involved.

Two pharmacists and a pharmacy resident will participate in each phase.

The following table (Table 2) describes the research procedures and activities in the two phases.

Timepoint	*Research steps*	Observational phase	Interventional phase
HOSPITALIZATION	***PICC line prescription***	Screening: Eligibility assessment	
	Intervention scheduled	Enrollment: Informed consent	
	PICC line indication	Document purpose and duration of catheterization	
			Pharmaceutical analysis to identify errors or potentially inappropriate prescriptions[1]; discussion with prescribers; pharmaceutical interventions in the event of unjustified deviation from existing guidelines
	In the operating room (OR) before the implantation	Verify that all necessary equipment is available for the surgery	
			Help with ordering if necessary
		Conformity assessment of the expiration date for all PICC lines stored in the OR's supply room	
			Help with ordering if necessary. Rationalization of the medical device stock if necessary
		Conformity assessment of traceability from receipt of the medical device order by the pharmacy to delivery to the care unit	
			Corrections if necessary
	Implantation of PICC line = day 0	Number of medical devices used during the operation (implantation failures or non-functional devices)	
		Implantation traceability to ensure lot numbers match in the patient's record, the OR book and the computer software	
			Corrections if necessary
	Remainder of the hospitalization	Record possible complications during the remainder of the hospital stay	
			Corrections and help if complications occur
DISCHARGE	***Discharge prescription***	Pharmaceutical analysis of the patient's discharge order. The analysis will focus on drugs and MDs related to the PICC line (e.g. dressing repair set). Conformity analysis of the hospital prescriptions issued by local pharmacy	
			Pharmaceutical analysis of the patient's discharge order and optimization[1] if necessary. Discussion with the physician and correction
	Patient discharge	Quality of Life assessment (EQ5D5L scale)	
			Pharmaceutical interview with the patient:

			Discuss the different treatments on the discharge order, answer any questions. Provide information about the PICC line, how to use it, maintain it and how to detect potential complications. Make sure that traceability documents are provided. Make sure that the PICC line's user booklet is provided. Transmission of the discharge order to the community pharmacist.
PRIMARY CARE	***Day 3*** ***Day 7***	Phone calls to collect complications or any events regarding the PICC line and drugs -Patient -Private nurse	
			Provide personalized and appropriate advice Pharmaceutical interventions if necessary
	M1, M2	Phone calls to collect complications or any events regarding the PICC line and drugs: -Patient -Private nurse Phone calls to community pharmacist to record information related to care consumption	
			Provide personalized and appropriate advice Pharmaceutical interventions if necessary
	M3	Quality of Life assessment (EQ5D5L scale) Phone calls to collect complications or any events regarding the PICC line and drugs: -Patient -Private nurse -Community pharmacist to record information related to care consumption -General practitioner to identify any consultations related to the PICC line and any other relevant information Sooner if there is a need to confirm clinical data on complications such as thrombotic events.	

Table 2: Detailed research process. [1]According to the gold standard or START and STOPP method(34) *or European PIM list*(35) *for older adults*

At the end of the study, a satisfaction survey will be sent to every participant (patients and caregivers).

Outcomes and expected benefits

Primary outcome

The primary outcome is the number of complications per patient and per month. Complications will be documented on specific forms to harmonize data collection. Mechanical complications are defined as obstruction or occlusion (18), breakage or damage to the catheter(27), migration (36), or dislodgment (accidental withdrawal) of the catheter(37). Clinical complications are defined as redness around the insertion site (diameter > 2 cm), edema (size difference between the two hands), pain (numeric rating scale), fever (internal temperature > 37°C) as signs of an infection(17,38) and thrombotic events(39) (confirmed by a medical modality such as echography).

Secondary outcomes

The number of consultations and rehospitalizations post-discharge will be used to determine the clinical impact beyond the initial hospitalization (11,40–42). The expected result is a decrease in the consultation and rehospitalization rates at the end of the intervention phase compared to the observation phase.

The acceptance rate of pharmaceutical interventions during the interventional phase is used to assess the appropriateness of pharmaceutical interventions (43–47). A higher acceptance rate means the pharmaceutical interventions are justified and relevant to the care providers. The criticality of the pharmacist's intervention (48) will be evaluated. Moreover, conformity of the hospital prescriptions for primary care after the discharge will be assessed. The aim is to avoid treatment breaks.

Another secondary outcome involves the conformity analysis of the PICC line logistics circuit (checklist related to stock, supply chain, traceability). Management of the hospital supply chain is a major financial challenge (49) and generally leads to decreased treatment risk and costs (50). The objective is to streamline the various stages of the PICC line logistics circuit, from ordering to implantation. By streamlining the logistics, improved patient safety and reduced costs are expected.

The conformity of the PICC line indication will be evaluated according to recommendations(51). Prescriptions too often seem to be trivialized and little guided by attending doctors. Therefore, errors are possible. The aim is to improve the team's knowledge and the communication between hospital units.

The patients' quality of life before and after the follow-up will be measured with the EQ5D5L scale (52). A score of five corresponds to the best possible quality of life whereas 25 is the worst possible score. An improvement in the quality of life score is expected during the intervention phase.

Satisfaction of the patients and the healthcare providers involved will be evaluated. To develop clinical pharmacy activities in health care services, collaboration and communication with health care teams is essential.

The direct hospital costs will be estimated and described. The objective is to estimate whether additional costs are induced, or whether costs are spared through better organization and logistics management (53).

Statistical analysis

Sample Size Calculation

According to the ENEIS studies (2004 and 2009) and their final report (54), at least 50% of iatrogenic serious adverse events are preventable whether due to medications or MDs. Assuming that clinical pharmacy integration could theoretically lead to a 25% decrease in the complication rate during the interventional phase, 62 patients are needed in each group (80% power, alpha 5%). Thus, 138 patients need to be recruited assuming that 10% are lost to follow-up. All early exits from the study will be considered as lost to follow-up and the affected data will be processed in the statistical analysis as intent-to-treat.

Statistics

Statistical tests will be used that are appropriate for the distribution of the variables. All tests will be performed at an alpha risk of 5%. Categorical variables will be described by counts and percentages.

Means and standard deviations will be reported for continuous variables with normal distribution, and median and quartiles for other continuous variables.

Patient demographics and clinical characteristics will be described.

To assess the effectiveness of the intervention, means or medians of the number of complications per month and per patient for each phase will be estimated and a Poisson regression will be used. An adjustment for confounding factors such as sex, age and Charlson Comorbidity Index is planned.

The secondary outcomes will be analyzed as described in Table 3**Error! Reference source not found.**.

Variables types	Variables of interest	Description	Tests
Quantitative	• Consultations and rehospitalizations after discharge • EQ5D5L scores • Direct hospital costs	Means ± Standard Deviation (SD) or Medians and quartiles	Student's *t* test or non-parametric Wilcoxon's test
Qualitative	• Conformity rates (logistics, indications for implantation and prescriptions issued by local pharmacy) • Satisfaction levels	Percentages Rates	Chi^2 test or Fisher's exact test

Table 3 : Statistical analysis for the secondary outcomes

Discussion

The main objective is to demonstrate the effectiveness of clinical pharmacy activities in preventing complications in patients implanted with a PICC line. This is a strong clinical criterion. There is abundant literature about the occurrence of complications following the insertion of a PICC line, in a hospital (20–24) or at home(27,55,56). At the same time, reported rates vary widely across studies. These rates were pooled to estimate an "average" complication rate. This method was used to calculate the number of subjects needed for this study. These assumptions have an impact on the robustness of the study and may require the use of statistical adjustments when analyzing the results. As for complications, the numbers of consultations and rehospitalizations post-discharge have been used in several studies, particularly the 30-day readmission rate (11,42,57–59) to assess the clinical effectiveness of a pharmacist's interventions. Despite the wide assortment of these rates in the literature, this indicator is relevant for comparing our study to others. However, it will be difficult to obtain exhaustive results, as the data will be derived from statements made by the different participants. The information will only be formally verifiable if the patient in question is readmitted or consults in one of our hospital's departments.

The acceptance rate of pharmaceutical interventions is not only a widely used and recognized indicator (43,60) for assessing the appropriateness of interventions, it is also an indicator routinely used in hospitals. A conformity analysis of the hospital prescriptions for primary care is one of the secondary endpoints. It seems essential to secure these prescriptions also because the patient's transition is known to be a high risk event (61). Good clinical practices allow health professionals to decrease errors and avoid potential errors in prescription. Iatrogenic events are associated with additional costs (62). A checklist of items was developed to evaluate the conformity of the PICC line's logistics circuit. This list is particularly exhaustive and will be used by all those who collect data. This will avoid an evaluation bias that could be linked to the large number of healthcare providers involved. The checklist will help to identify the most common errors or pitfalls encountered and to establish adequate corrective measures. Current guidelines are available for the device's logistics (51).

The prospective study design allows to assess the patients' quality of life using the EQ-5D-5L Scale before and after the intervention. This criterion is needed to assess the patient's point of view, as the patient is the central element in the care pathway. To avoid interference or influence due to the presence of pharmacists, they will not to be present at the time of the first evaluation (day of discharge). However, the subsequent assessments will be done by telephone, thus pharmacists could influence patient responses. Likert scales have been developed to collect patient and healthcare professional satisfaction data (63). These tools are valid and reliable for collecting the opinions of different research participants. These scales capture more nuanced opinions, help to better understand the feedback and to identify areas for improvement. The various parties involved generally appreciate these tools. It should not be particularly difficult to collect and analyze these results. Nevertheless, different patients will enrolled during the observational and interventional phases. Consequently, the differences in satisfaction, if any, may also be due to a difference in individuals between the two groups. A low response rate from professionals to the satisfaction survey is expected, as described in the literature (64).

This study involves only one hospital and focuses on one type of implantation. This is a preliminary study before scaling up a larger, multi-center and randomized trial with several implantable medical devices (IMDs). This future study will follow a stepped-wedge method consisting of randomization by center and not by patient for the deployment of before-and-after phases in each of the participating centers. This study is a major step towards evaluating the efficacy of clinical pharmacy applied to IMDs with the aim of a larger-scale study with valuable randomization. At this moment, the before-after design appears to be the closest to the stepped-wedge method since they share separate observational and interventional periods. Indeed, randomization is not possible given the nature of the intervention and the high risk of contamination bias. This point is critical. Moreover, the measurement and analysis of costs is limited to direct hospital medical costs, which does not allow an overall analysis of the costs of care. Additional health economics analyses are planned for the multicenter study.

This study will investigate the impact of the integration of clinical pharmacy activities during the overall care pathway. This is the first step towards a change in practices, improved communication between professionals, better collaboration and the integration of a clinical pharmacist into multidisciplinary teams, including surgical ones. This study is the first, to our knowledge, to focus on clinical pharmacy for implantable MDs with a hard, clinical endpoint.

Potential limitations and bias

Since the study is not randomized, the selection bias and two non-comparable samples are risky. To overcome this limitation, an adjustment on the main confounding factors (such as age, sex and comorbidity index) will be considered.

Blinding is not possible due to the nature of the intervention. To limit a measurement bias, a blind methodologist will analyze the primary endpoint.

Recruitment may take longer than expected because all the PICC lines are placed in the operating room and are not a priority as opposed to life-threatening emergencies.

Phone calls to collect clinical data on complications, deaths and rehospitalizations are limited. The collected data is based solely on the patients' and care providers' statements. It is possible that they may intentionally or unintentionally omit some information. The plurality of involved counterparts may help to corroborate the given information. Data collection will be harmonized by double-checking the collection forms and the information collected at the time of the pharmaceutical interviews and phone calls.

Trial status

National registration number: 2019-A02475-52

Clinical Trials registration number: NCT04359056

Abbreviations

ENEIS: Enquête nationale sur les évènements indésirables graves associés aux soins (National French Adverse Events Study)

HAS: Haute Autorité de Santé (French National Authority for Health)

Figure legends

Figure 1: Study design.

Authors' statement

Alix Marie POUGET, Elodie CIVADE and Charlotte ROUZAUD-LABORDE contributed to the conception of the study. The authors will be responsible for the acquisition and analysis of the data, interpretation and dissemination of the results.

Alix Marie POUGET and Charlotte ROUZAUD-LABORDE contributed to the draft of this protocol.

Alix Marie POUGET, Elodie CIVADE, Philippe CESTAC and Charlotte ROUZAUD-LABORDE contributed to the revision of this protocol and approved the final version to be published.

All authors have agreed to be accountable for all aspects of the study such as accuracy and integrity of the work.

Author's declarations

There is no personal data in the protocol.

Additional data and materials are not available except through the corresponding author.

The authors do not declare any conflict of interest.

Sponsor

The Research and Innovation Board of the Toulouse University Hospital Center is the sponsor of this study. The protocol is locally registered with the following number: RC31/18/0459.

Funding

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Ethics and dissemination

The regional French Ethics Committee (CPP South-East VI, Clermont-Ferrand, France) assessed the scientific ethics of the protocol (version dated 3 February 2020) and approved this study.

All data collected will be anonymized and access to the data will be restricted to those participating in the research (investigators, pharmacists and pharmacy residents).

The results of the study will be published when available.

Acknowledgements

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References

1. Société Française de Pharmacie Clinique (SFPC). Présentation de la Pharmacie Clinique [Internet]. 2016. Available from: http://sfpc.eu/fr/la-sfpc/presentation.html
2. Jack BW, Chetty VK, Anthony D, Greenwald JL, Sanchez GM, Johnson AE, et al. A Reengineered Hospital Discharge Program to Decrease Rehospitalization: A Randomized Trial [Internet]. 2009 [cited 2019 Dec 2]. Available from: www.annals.org.
3. Pal A, Babbott S, Wilkinson ST. Can the targeted use of a discharge pharmacist significantly decrease 30-day readmissions? Hosp Pharm. 2013 May 1;48(5):380–8.
4. McKay C, Park C, Chang J, Brackbill M, Choi JY, Lee JH, et al. Systematic Review and Meta-analysis of Pharmacist-Led Transitions of Care Services on the 30-Day All-Cause Readmission Rate of Patients with Congestive Heart Failure. Vol. 39, Clinical Drug Investigation. Springer International Publishing; 2019. p. 703–12.
5. Renaudin P, Boyer L, Esteve M-A, Bertault-Peres P, Auquier P, Honore S. Do pharmacist-led medication reviews in hospitals help reduce hospital readmissions? A systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82(6):1660–73.
6. Haute Autorité de Santé - Mettre en œuvre la conciliation des traitements médicamenteux en établissement de santé [Internet]. [cited 2019 Dec 2]. Available from: https://www.has-sante.fr/jcms/c_2736453/fr/mettre-en-oeuvre-la-conciliation-des-traitements-medicamenteux-en-etablissement-de-sante
7. Lipton HL, Bird JA. The Impact of Clinical Pharmacists' Consultations on Geriatric Patients' Compliance and Medical Care Use: A Randomized Controlled Trial. Gerontologist. 2011;34(3):307–15.
8. Sadik A, Yousif M, McElnay JC. Pharmaceutical care of patients with heart failure. Br J Clin Pharmacol. 2005;60(2):183–93.
9. Leguelinel-Blache G, Arnaud F, Bouvet S, Dubois F, Castelli C, Roux-Marson C, et al. Impact of

admission medication reconciliation performed by clinical pharmacists on medication safety. Eur J Intern Med [Internet]. 2014;25(9):808–14. Available from: http://dx.doi.org/10.1016/j.ejim.2014.09.012

10. Lehnbom EC, Stewart MJ, Manias E, Westbrook JI. Impact of Medication Reconciliation and Review on Clinical Outcomes. Ann Pharmacother. 2014;48(10):1298–312.
11. Mekonnen AB, McLachlan AJ, Brien JAE. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: A systematic review and meta-analysis. Vol. 6, BMJ Open. BMJ Publishing Group; 2016.
12. Daliri S, Hugtenburg JG, Ter Riet G, Van den Bemt BJF, Buurman BM, Scholte op Reimer WJM, et al. The effect of a pharmacy-led transitional care program on medication-related problems post-discharge: A before—After prospective study. PLoS One. 2019 Mar 1;14(3).
13. Ferrand E, Painchart L, Grimandi G, Décaudin B, Bussières J. Rôles et retombées des pharmaciens dans la gestion des dispositifs médicaux en établissement de santé : une revue de littérature. Ann Pharm Fr [Internet]. 2017; Available from: http://dx.doi.org/10.1016/j.pharma.2017.05.001
14. Painchart L, Drancourt P, Aubert J, Inghels Y, Boyer J. Interest and difficulties in setting up pharmaceutical reconciliations for patients with dressings for complex wounds. Ann Pharm Fr. 2019;
15. Kumar A, Kethireddy S, Darovic GO. Catheter-related and infusion-related sepsis. Vol. 29, Critical Care Clinics. Crit Care Clin; 2013. p. 989–1015.
16. Rupp ME, Karnatak R. Intravascular Catheter–Related Bloodstream Infections. Vol. 32, Infectious Disease Clinics of North America. W.B. Saunders; 2018. p. 765–87.
17. Lee JH, Kim ET, Shim DJ, Kim IJ, Byeon JH, Lee IJ, et al. Prevalence and predictors of peripherally inserted central catheter-associated bloodstream infections in adults: A multicenter cohort study. PLoS One. 2019;14(3).
18. Bartock L. An Evidence-Based Systematic Review of Literature for the Reduction of PICC Line

Occlusions. J Assoc Vasc Access [Internet]. 2010;15(2):58–63. Available from: http://dx.doi.org/10.2309/java.15-2-3

19. Grove JR, Pevec WC. Venous thrombosis related to peripherally inserted central catheters. J Vasc Interv Radiol. 2000;11(7):837–40.

20. Cowl CT, Weinstock J V., Al-Jurf A, Ephgrave K, Murray JA, Dillon K. Complications and cost associated with parenteral nutrition delivered to hospitalized patients through either subclavian or peripherally-inserted central catheters. Clin Nutr. 2000;19(4):237–43.

21. Amerasekera SSH, Jones CM, Patel R, Cleasby MJ. Imaging of the complications of peripherally inserted central venous catheters. Clin Radiol [Internet]. 2009;64(8):832–40. Available from: http://dx.doi.org/10.1016/j.crad.2009.02.021

22. Leroyer C, Lashéras A, Marie V, Le Bras Y, Carteret T, Dupon M, et al. Prospective follow-up of complications related to peripherally inserted central catheters. Med Mal Infect [Internet]. 2013;43(8):350–5. Available from: http://dx.doi.org/10.1016/j.medmal.2013.06.013

23. Greene MT, Flanders SA, Woller SC, Bernstein SJ, Chopra V. The Association between PICC Use and Venous Thromboembolism in Upper and Lower Extremities. Am J Med. 2015;128(9).

24. Bertoglio S, Faccini B, Lalli L, Cafiero F, Bruzzi P. Peripherally inserted central catheters (PICCs) in cancer patients under chemotherapy: A prospective study on the incidence of complications and overall failures. J Surg Oncol. 2016;113(6).

25. Jones D, Wismayer K, Bozas G, Palmer J, Elliott M, Maraveyas A. The risk of venous thromboembolism associated with peripherally inserted central catheters in ambulant cancer patients. Thromb J. 2017;15(1):1–6.

26. Grau D, Clarivet B, Lotthé A, Bommart S, Parer S. Complications with peripherally inserted central catheters (PICCs) used in hospitalized patients and outpatients: A prospective cohort study. Antimicrob Resist Infect Control [Internet]. 2017;6(1):1–8. Available from: http://dx.doi.org/10.1186/s13756-016-0161-0

27. Opilla M. Peripherally Inserted Central Catheter Experience in Long-Term Home Parenteral

Nutrition Patients. JAVA - J Assoc Vasc Access [Internet]. 2017;22(1):42–5. Available from: http://dx.doi.org/10.1016/j.java.2016.12.001

28. Société Française d'Hygiène Hospitalière (SF2H). Bonnes Pratiques Et Gestion Des Risques Associés Au Picc -Hygiènes -Volume Xxi -N° 6. 2013; Available from: https://sf2h.net/wp-content/uploads/2014/05/SF2H_bonnes-pratiques-et-gestion-des-risques-associes-au-PICC-2013.pdf

29. Gallagher J, McCarthy S, Byrne S. Economic evaluations of clinical pharmacist interventions on hospital inpatients: a systematic review of recent literature. Int J Clin Pharm. 2014;36(6):1101–14.

30. Lawson EH, Hall BL, Louie R, Ettner SL, Zingmond DS, Han L, et al. Association between occurrence of a postoperative complication and readmission: Implications for quality improvement and cost savings. Ann Surg. 2013;258(1):10–8.

31. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: Defining standard protocol items for clinical trials. Vol. 158, Annals of Internal Medicine. American College of Physicians; 2013. p. 200–7.

32. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;

33. Dale A, Copeland R, Barton R. Prescribing errors on medical wards and the impact of clinical pharmacists. Int J Pharm Pract. 2005;11(1):19–24.

34. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72–83.

35. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol [Internet]. 2015 Jul 14 [cited 2020 Feb 24];71(7):861–75. Available from: http://link.springer.com/10.1007/s00228-015-1860-9

36. Haygood TM, Malhotra K, Ng C, Chasen B, McEnery KW, Chasen M. Migration of central lines from the superior vena cava to the azygous vein. Clin Radiol. 2012;67(1):49–54.

37. Moureau N. Impact and Safety Associated with Accidental Dislodgement of Vascular Access Devices: A Survey of Professions, Settings, and Devices. JAVA - J Assoc Vasc Access [Internet]. 2018;23(4):203–15. Available from: https://doi.org/10.1016/j.java.2018.07.002

38. Chopra V, Anand S, Krein SL, Chenoweth C, Saint S. Bloodstream infection, venous thrombosis, and peripherally inserted central catheters: Reappraising the evidence. Am J Med [Internet]. 2012;125(8):733–41. Available from: http://dx.doi.org/10.1016/j.amjmed.2012.04.010

39. Fallouh N, McGuirk HM, Flanders SA, Chopra V. Peripherally inserted central catheter-associated deep vein thrombosis: A narrative review. Am J Med. 2015;128(7).

40. Unplanned hospital visits [Internet]. [cited 2019 Dec 23]. Available from: https://www.medicare.gov/hospitalcompare/Data/Hospital-returns.html

41. Koehler BE, Richter KM, Youngblood L, Cohen BA, Prengler ID, Cheng D, et al. Reduction of 30-day postdischarge hospital readmission or emergency department (ED) visit rates in high-risk elderly medical patients through delivery of a targeted care bundle. J Hosp Med. 2009;4(4):211–8.

42. Hohl CM, Partovi N, Ghement I, Wickham ME, McGrail K, Reddekopp LN, et al. Impact of early in-hospital medication review by clinical pharmacists on health services utilization. PLoS One. 2017;12(2):1–13.

43. Bedouch P, Charpiat B, Conort O, Rose FX, Escofier L, Juste M, et al. Assessment of clinical pharmacists' interventions in French Hospitals: Results of a multicenter study. Ann Pharmacother. 2008 Jul;42(7–8):1095–103.

44. Charpiat B, Bedouch P, Conort O, Rose FX, Juste M, Roubille R, et al. Opportunités d'erreurs médicamenteuses et interventions pharmaceutiques dans le cadre de la prescription informatisée : Revue des données publiées par les pharmaciens hospitaliers français. Vol. 70, Annales Pharmaceutiques Francaises. 2012. p. 62–74.

45. Charpiat B, Conort O, Juste M, Rose FX, Roubille R, Bedouch P, et al. Mise à disposition de l'outil de codification des interventions pharmaceutiques de la Société française de pharmacie clinique : bilan à 10 ans et perspectives. Vol. 50, Pharmacien Hospitalier et Clinicien. Elsevier Masson SAS; 2015. p. e15–24.

46. Mongaret C, Quillet P, Vo TH, Aubert L, Fourgeaud M, Michelet-Huot E, et al. Predictive factors for clinically significant pharmacist interventions at hospital admission. Vol. 97, Medicine (United States). Lippincott Williams and Wilkins; 2018.

47. Aguiar K da S, Santos JM Dos, Cambrussi MC, Picolotto S, Carneiro MB. Patient safety and the value of pharmaceutical intervention in a cancer hospital. Einstein (Sao Paulo). 2018;16(1):eAO4122.

48. Ha Vo T. Evaluation of the potential impact of pharmacist interventions : development and validation of the CLEO multidimensional tool [Internet]. [cited 2020 Feb 24]. Available from: https://tel.archives-ouvertes.fr/tel-01315619

49. Moons K, Waeyenbergh G, Pintelon L. Measuring the logistics performance of internal hospital supply chains – A literature study. Omega (United Kingdom) [Internet]. 2019;82:205–17. Available from: https://doi.org/10.1016/j.omega.2018.01.007

50. Chasseigne V, Leguelinel-Blache G, Nguyen TL, de Tayrac R, Prudhomme M, Kinowski JM, et al. Assessing the costs of disposable and reusable supplies wasted during surgeries. Int J Surg [Internet]. 2018;53:18–23. Available from: https://doi.org/10.1016/j.ijsu.2018.02.004

51. Société Française d'Hygiène Hospitalière (SF2H). Good practice and risk management for the use of PICC. 2013;(December).

52. Redmond P, Grimes TC, Mcdonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. Vol. 2018, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2018.

53. Chasseigne V, Bouvet S, Chkair S, Buisson M, Richard M, de Tayrac R, et al. Health economic evaluation of a clinical pharmacist's intervention on the appropriate use of devices and cost

savings: A pilot study. Int J Surg. 2020;82(July):143–8.

54. Michel P, Lathelize M, Bru-Sonnet R, Perez C, Domecq S, Kret M, et al. Rapport final - Comparaison des deux études ENEIS 2004 et 2009. Drees, Ministère la santé. 2011;1–118.

55. Christensen LD, Holst M, Bech LF, Drustrup L, Nygaard L, Skallerup A, et al. Comparison of complications associated with peripherally inserted central catheters and Hickman™ catheters in patients with intestinal failure receiving home parenteral nutrition. Six-year follow up study. Clin Nutr [Internet]. 2016;35(4):912–7. Available from: http://dx.doi.org/10.1016/j.clnu.2015.06.009

56. Santacruz E, Mateo-Lobo R, Riveiro J, Nattero L, Vega-Piñero B, Lomba G, et al. Infectious complications in home parenteral nutrition: A long-term study with peripherally inserted central catheters, tunneled catheters, and ports. Nutrition. 2019;58:89–93.

57. Kilcup M, Schultz D, Carlson J, Wilson B. Postdischarge pharmacist medication reconciliation: Impact on readmission rates and financial savings. J Am Pharm Assoc. 2013;53(1):78–84.

58. Jones CD, Anthony A, Klein MD, Shakowski C, Smith HK, Go A, et al. The effect of a pharmacist-led multidisciplinary transitions-of-care pilot for patients at high risk of readmission. J Am Pharm Assoc. 2018 Sep 1;58(5):554–60.

59. Lussier ME, Evans HJ, Wright EA, Gionfriddo MR. The impact of community pharmacist involvement on transitions of care: A systematic review and meta-analysis. J Am Pharm Assoc [Internet]. 2019; Available from: https://doi.org/10.1016/j.japh.2019.07.002

60. Leguelinel-Blache G, Castelli C, Roux-Marson C, Bouvet S, Andrieu S, Cestac P, et al. Impact of collaborative pharmaceutical care on in-patients' medication safety: Study protocol for a stepped wedge cluster randomized trial (MEDREV study). Trials. 2018 Jan 8;19(1).

61. Ensing HT, Stuijt CCM, Van Den Bemt BJF, Van Dooren AA, Karapinar-Çarkit F, Koster ES, et al. Identifying the optimal role for pharmacists in care transitions: A systematic review. Vol. 21, Journal of Managed Care Pharmacy. Academy of Managed Care Pharmacy (AMCP); 2015. p. 614–38.

62. Rigby K. Adverse events in health care: Setting priorities based on economic evaluation. J Qual Clin Pract. 1999;19(1):7–12.

63. Likert R. A technique for the measurement of attitudes. Arch Psychol. 1932;22(140):55.

64. Cook J V., Dickinson HO, Eccles MP. Response rates in postal surveys of healthcare professionals between 1996 and 2005: An observational study. BMC Health Serv Res. 2009;9:1–8.

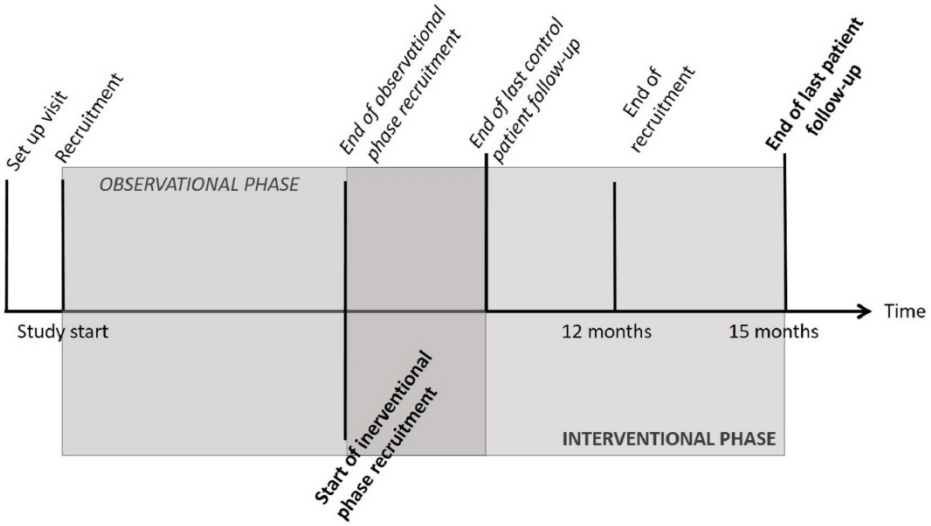

Figure 1: Study design.

159x91mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 15
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data	16

		management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3, 4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4,5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5,6,7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7,8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9,10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, 7-8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4,5
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4, 14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	blinding is not possible in this study except for analysis

Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13,14

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10,11,12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10,11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods:			
Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	before-after study: interim analysis not necessary

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5-8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A, no ancillary studies planned

Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A , no ancillary trials.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16, all supplementary data through corresponding author
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	4, model as supplementary files
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A, no biological specimens

Notes:

- 11a: 8, 9, 10, 11, 12
- 17b: blinding is not possible in this study exept for analysis
- 21b: before-after study: interim analysis not necessary
- 26b: N/A, no ancillary studies planned
- 30: N/A , no ancillary trials.
- 31c: 24, all supplementary data through corresponding author
- 32: documents approuved by the ethic committee (24)

- 33: N/A, no biological specimens This checklist was completed on 07. April 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

From hospitalization to primary care, integrative model of clinical pharmacy with patients implanted with a PICC line: research protocol for a prospective before-after study.

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Primary Subject Heading:	Pharmacology and therapeutics
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Keywords:	CLINICAL PHARMACOLOGY, Clinical trials < THERAPEUTICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

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From hospitalization to primary care, integrative model of clinical pharmacy with patients implanted with a PICC line: research protocol for a prospective before-after study

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Trial acronym: CLIPICC

Abstract

Introduction

Clinical pharmacy improves patient safety and secures drug management using information, education and good clinical practices. However, medical device management is still unexplored, and proof of effectiveness is needed. A PICC line is a medical device for infusion. It accesses the central venous system after being implanted in a peripheral vein. But complications after implantation often interfere with smooth execution of the treatment. We hypothesize that clinical pharmacy for medical devices could be as effective as clinical pharmacy for medications. The main objective is to assess the effectiveness of clinical pharmacy activities on the complication rate after PICC line implantation.

Methods and analysis

This is a before-after prospective study. The study will begin with an observational period without clinical pharmacy activities, followed by an interventional period where pharmacists will intervene on drug and medical device management and provide personalized follow-up and advice. Sixty-nine adult patients will be recruited in each 6-month period from all traditional care units. The main inclusion criteria will be the implantation of a PICC line. The primary outcome is the decrease in the number of complications per patient and per month. Secondary outcomes are the consultation and hospital readmission rates, the acceptance rate of pharmaceutical interventions, the patients' quality of life, the direct hospital induced or avoided costs and the participants' satisfaction. Data will be collected using Case Report Forms during hospitalization and telephone follow-up after discharge. The analysis will compare these criteria during the two periods.

Ethics and dissemination

The study has received the approval of our Ethics Committee (Clermont-Ferrand Southeast VI, France, number AU1586). Results will be made available to the patients or their caregivers, the sponsor and other researchers when asked, as described in the consent form.

Trial registration

2019-A02475-52 (ID-RCB number)
ClinicalTrials.gov*:* NCT04359056

Keywords

Clinical Pharmacy, Medical Devices, PICC lines, Protocol, Before-After Study

Strengths and Limitations

- This is the first study to assess the effectiveness of clinical pharmacy interventions for medical devices. The literature essentially works with medications, when medical devices are explored with pharmacist's activities; the patient impact is not evaluated.

- Strong clinical criteria will be evaluated by measuring skin redness, edema, thrombosis and pain. Our study does not measure intermediate criteria as a primary objective, such as the number of potentially inappropriate prescriptions.

- This study proposes an integrative model of clinical pharmacy, from hospitalization to primary care.

- The main limitations of this study are the lack of randomization and the lack of blinding for patients and healthcare professionals.

Introduction

Clinical pharmacy is a patient-centered health discipline whose practice aims to optimize therapy at each stage of the care pathway. Clinical pharmacy actions contribute to patient safety and the relevant and efficient use of health products (1). To ensure health products are used in a safe and appropriate manner, pharmacists analyze physicians' orders to identify errors or potentially inappropriate prescriptions based on guidelines and evidence-based medicine. Moreover, they optimize drug intake, inform patients and caregivers, organize the discharge to primary care and disseminate clinical good practices. Pharmacists also focus on patient education, information, and training for healthcare professionals.

Regarding medication approaches, the effectiveness of clinical pharmacy is well known. Several clinical studies have demonstrated significant impacts on re-hospitalizations (2–5), drug management (6) and treatment compliance (7), patients' quality of life(8) as well as a decrease of iatrogenic risk (9–12). But studies on clinical pharmacy in the context of medical devices (MD) are rare (13). To our knowledge, no study has described the clinical impact of a pharmacist's intervention when a MD is implanted in patients. Only one recent article refers to clinical pharmacy in dressings for complex wounds (14). The need for further clinical studies is undeniable.

MD classification is based on their risk of invasiveness and duration of use. Infusion equipment, such as catheters, can induce iatrogenic events, especially infections (15,16). Peripherally inserted central catheters (PICC lines) are associated with numerous clinical (e.g. infections (17)) and mechanical complications (e. g. catheter occlusions (18)) (19–27). PICC lines are useful for the administration of irritating products or for the repeated collection of blood samples. PICC lines are recommended when the duration of catheterization ranges from 7 days to 3 months (28). PICC line implantations are carried out in the interventional radiology operating room.

Our working hypothesis is that clinical pharmacy interventions will prevent clinical and mechanical complications and thereby reduce hospital costs(29). Reducing complications could also prevent its consequences such as rehospitalizations (30) and physician visits.

Methods and Analysis

A scientific committee (selected by the Research and Innovation Board of the Toulouse University Hospital) composed of scientific and methodological experts and statisticians oversaw the feasibility and methodology of the study. This committee ensures the quality and relevance of the research organization. The study procedures and assessments comply with the Standard Protocol Items: Recommendations for Interventional Trials (31).

Design

A pragmatic single center design is used. This is a before-after prospective study with two consecutive phases: observational (no clinical pharmacy activities) and interventional (execution of clinical pharmacy activities and logistics optimization). Randomization of patients is not possible in this study due to the high risk of contamination bias. Once the clinical pharmacist arrives in the care unit, he or she should address any medical apprehension by the PICC prescribers and nurses, explaining good clinical use, affecting all the future study patients, even the control group. This is an open study. Due to the nature of the pharmaceutical interventions, blinding is not possible for patients and care providers.

Setting

The study will take place in the Toulouse University Hospital Center. Every PICC line prescription will be picked up in the interventional radiology unit and patients will be screened for eligibility. Patients will be recruited from their hospital ward prior to the PICC line insertion. All selected participants will be asked to read and sign a consent form. Each phase (observational and interventional) will last

approximately 9 months taking into account recruitment and patient follow-up. See Figure 1 for the study timeline.

Recruitment began on Monday, May 25, 2020 and will end 1 year later on May 25, 2021. The study is scheduled to end on August 25, 2021.

Characteristics of participants: Inclusion and exclusion criteria

Eligibility criteria are listed in Table 1. For all included patients, the Charlson Comorbidity Index (32) will be use to assess the degree of comorbidity at baseline.

Inclusion criteria	Adult patient, 18 years of age or older Patient capable of giving free and informed consent Patient insured by the Social Security System in France Patient living at home Patient with a PICC line prescription Patient whose discharge prescription should contain drugs and MDs Patient for home discharge implanted with a PICC line Patient reachable by phone
Exclusion criteria	Under-aged patient, less than 18 years old Patient not insurance by the Social Security System in France Patient not living at home: Institutionalized patient Patient living in a facility for elderly dependent persons Nursing home resident “Hospital at Home” patient Patient deprived of their freedom by a judicial or administrative decision Patient under guardianship, curatorship or safeguard of justice Patient unreachable by phone Pregnant or breastfeeding women

Table 1 : Inclusion and exclusion criteria

Patient and public involvement

No patient involved.

Process

Regardless of the phase of the study, the occurrence of complications due to the PICC line will be recorded during hospitalization and at home during a follow-up phone call. Patients are monitored for the entire duration of the PICC line implantation or for a maximum of 3 months. Data will be collected at days 3 and 7 (D3 or D7 respectively) after implantation and then after 1, 2 and 3 months (M1, M2 and M3 respectively).

The control period corresponds to usual care and represents the observational phase, where no pharmaceutic interventions will be done, unless necessary for the patient's safety (e.g. life-threatening situations(33)).

One participant can be included in only one phase. The interventional phase will start when the last patient is included in the observational phase. Physicians and nurses, as well as other healthcare professionals, will attend training sessions on updates, recommendations, indications, and maintenance related the use of PICC lines. If necessary, training sessions will be repeated once to make sure the research team met all the healthcare professionals involved.

Two pharmacists and a pharmacy resident will participate in each phase.

The following table (Table 2) describes the research procedures and activities in the two phases.

Timepoint	*Research steps*	Observational phase	Interventional phase
HOSPITALIZATION	***PICC line prescription***	Screening: Eligibility assessment	
	Intervention scheduled	Enrollment: Informed consent	
	PICC line indication	Document purpose and duration of catheterization	
			Pharmaceutical analysis to identify errors or potentially inappropriate prescriptions[1]; discussion with prescribers; pharmaceutical interventions in the event of unjustified deviation from existing guidelines
	In the operating room (OR) before the implantation	Verify that all necessary equipment is available for the surgery	
			Help with ordering if necessary
		Conformity assessment of the expiration date for all PICC lines stored in the OR's supply room	
			Help with ordering if necessary. Rationalization of the medical device stock if necessary
		Conformity assessment of traceability from receipt of the medical device order by the pharmacy to delivery to the care unit	
			Corrections if necessary
	Implantation of PICC line = day 0	Number of medical devices used during the operation (implantation failures or non-functional devices)	
		Implantation traceability to ensure lot numbers match in the patient's record, the OR book and the computer software	
			Corrections if necessary
	Remainder of the hospitalization	Record possible complications during the remainder of the hospital stay	
			Corrections and help if complications occur
DISCHARGE	***Discharge prescription***	Pharmaceutical analysis of the patient's discharge order. The analysis will focus on drugs and MDs related to the PICC line (e.g. dressing repair set). Conformity analysis of the hospital prescriptions issued by local pharmacy	
			Pharmaceutical analysis of the patient's discharge order and optimization[1] if necessary. Discussion with the physician and correction
	Patient discharge	Quality of Life assessment (EQ5D5L scale)	
			Pharmaceutical interview with the patient:

			Discuss the different treatments on the discharge order, answer any questions. Provide information about the PICC line, how to use it, maintain it and how to detect potential complications. Make sure that traceability documents are provided. Make sure that the PICC line's user booklet is provided. Transmission of the discharge order to the community pharmacist.
PRIMARY CARE	***Day 3*** ***Day 7***	Phone calls to collect complications or any events regarding the PICC line and drugs -Patient -Private nurse	
			Provide personalized and appropriate advice Pharmaceutical interventions if necessary
	M1, M2	Phone calls to collect complications or any events regarding the PICC line and drugs: -Patient -Private nurse Phone calls to community pharmacist to record information related to care consumption	
			Provide personalized and appropriate advice Pharmaceutical interventions if necessary
	M3	Quality of Life assessment (EQ5D5L scale) Phone calls to collect complications or any events regarding the PICC line and drugs: -Patient -Private nurse -Community pharmacist to record information related to care consumption -General practitioner to identify any consultations related to the PICC line and any other relevant information Sooner if there is a need to confirm clinical data on complications such as thrombotic events.	

Table 2: Detailed research process. [1]According to the gold standard or START and STOPP method(34) *or European PIM list*(35) *for older adults*

At the end of the study, a satisfaction survey will be sent to every participant (patients and caregivers).

Outcomes and expected benefits

Primary outcome

The primary outcome is the number of complications per patient and per month. Complications will be documented on specific forms to harmonize data collection. Mechanical complications are defined as obstruction or occlusion (18), breakage or damage to the catheter(27), migration (36), or dislodgment (accidental withdrawal) of the catheter(37). Clinical complications are defined as redness around the insertion site (diameter > 2 cm), edema (size difference between the two hands), pain (numeric rating scale), fever (internal temperature > 37°C) as signs of an infection(17,38) and thrombotic events(39) (confirmed by a medical modality such as echography).

Secondary outcomes

The number of consultations and rehospitalizations post-discharge will be used to determine the clinical impact beyond the initial hospitalization (11,40–42). The expected result is a decrease in the consultation and rehospitalization rates at the end of the intervention phase compared to the observation phase.

The acceptance rate of pharmaceutical interventions during the interventional phase is used to assess the appropriateness of pharmaceutical interventions (43–47). A higher acceptance rate means the pharmaceutical interventions are justified and relevant to the care providers. The criticality of the pharmacist's intervention (48) will be evaluated. Moreover, conformity of the hospital prescriptions for primary care after the discharge will be assessed. The aim is to avoid treatment breaks.

Another secondary outcome involves the conformity analysis of the PICC line logistics circuit (checklist related to stock, supply chain, traceability). Management of the hospital supply chain is a major financial challenge (49) and generally leads to decreased treatment risk and costs (50). The objective is to streamline the various stages of the PICC line logistics circuit, from ordering to implantation. By streamlining the logistics, improved patient safety and reduced costs are expected.

The conformity of the PICC line indication will be evaluated according to recommendations(51). Prescriptions too often seem to be trivialized and little guided by attending doctors. Therefore, errors are possible. The aim is to improve the team's knowledge and the communication between hospital units.

The patients' quality of life before and after the follow-up will be measured with the EQ5D5Lquestionnaire (52). As previously described by Andrade et al. (53), a standard value set for converting the profiles on the 5 dimensions onto a score will be used.

An improvement in the quality of life score is expected during the intervention phase.

Satisfaction of the patients and the healthcare providers involved will be evaluated. To develop clinical pharmacy activities in health care services, collaboration and communication with health care teams is essential.

The direct hospital costs will be estimated and described. The objective is to estimate whether additional costs are induced, or whether costs are spared through better organization and logistics management (54).

Statistical analysis

Sample Size Calculation

According to the ENEIS studies (2004 and 2009) and their final report (55), at least 50% of iatrogenic serious adverse events are preventable whether due to medications or MDs. Assuming that clinical pharmacy integration could theoretically lead to a 25% decrease in the complication rate during the interventional phase, 62 patients are needed in each group (80% power, alpha 5%). Thus, 138 patients need to be recruited assuming that 10% are lost to follow-up. All early exits from the study will be considered as lost to follow-up and the affected data will be processed in the statistical analysis as intent-to-treat.

Statistics

Statistical tests will be used that are appropriate for the distribution of the variables. All tests will be performed at an alpha risk of 5%. Categorical variables will be described by counts and percentages. Means and standard deviations will be reported for continuous variables with normal distribution, and median and quartiles for other continuous variables.

Patient demographics and clinical characteristics will be described.

To assess the effectiveness of the intervention, means or medians of the number of complications per month and per patient for each phase will be estimated and a Poisson regression will be used. An adjustment for confounding factors such as sex, age and Charlson Comorbidity Index is planned.

The secondary outcomes will be analyzed as described in Table 3.

Table 3 : Statistical analysis for the secondary outcomes

Variables types	Variables of interest	Description*	Tests*
Quantitative	• Consultations and rehospitalizations after discharge • EQ5D5L scores • Direct hospital costs	Means ± Standard Deviation (SD) or Medians and quartiles Frequency table	Student's *t* test or non-parametric Wilcoxon's test
Qualitative	• Conformity rates (logistics, indications for implantation and prescriptions issued by local pharmacy) • Satisfaction levels	Frequency table	Chi^2 test or Fisher's exact test

*According to the distribution of variables.

Discussion

The main objective is to demonstrate the effectiveness of clinical pharmacy activities in preventing complications in patients implanted with a PICC line. This is a strong clinical criterion. There is abundant literature about the occurrence of complications following the insertion of a PICC line, in a hospital (20–24) or at home(27,56,57). At the same time, reported rates vary widely across studies. These rates

were pooled to estimate an "average" complication rate. This method was used to calculate the number of subjects needed for this study. These assumptions have an impact on the robustness of the study and may require the use of statistical adjustments when analyzing the results. As for complications, the numbers of consultations and rehospitalizations post-discharge have been used in several studies, particularly the 30-day readmission rate (11,42,58–60) to assess the clinical effectiveness of a pharmacist's interventions. Despite the wide assortment of these rates in the literature, this indicator is relevant for comparing our study to others. However, it will be difficult to obtain exhaustive results, as the data will be derived from statements made by the different participants. The information will only be formally verifiable if the patient in question is readmitted or consults in one of our hospital's departments.

The acceptance rate of pharmaceutical interventions is not only a widely used and recognized indicator (43,61) for assessing the appropriateness of interventions, it is also an indicator routinely used in hospitals. A conformity analysis of the hospital prescriptions for primary care is one of the secondary endpoints. It seems essential to secure these prescriptions also because the patient's transition is known to be a high risk event (62). Good clinical practices allow health professionals to decrease errors and avoid potential errors in prescription. Iatrogenic events are associated with additional costs (63).

A checklist of items was developed to evaluate the conformity of the PICC line's logistics circuit. This list is particularly exhaustive and will be used by all those who collect data. This will avoid an evaluation bias that could be linked to the large number of healthcare providers involved. The checklist will help to identify the most common errors or pitfalls encountered and to establish adequate corrective measures. Current guidelines are available for the device's logistics (51).

The prospective study design allows to assess the patients' quality of life using the EQ-5D-5L Scale before and after the intervention. This criterion is needed to assess the patient's point of view, as the patient is the central element in the care pathway. To avoid interference or influence due to the presence of pharmacists, they will not to be present at the time of the first evaluation (day of discharge). However, the subsequent assessments will be done by telephone, thus pharmacists could

influence patient responses. Likert scales have been developed to collect patient and healthcare professional satisfaction data (64). These tools are valid and reliable for collecting the opinions of different research participants. These scales capture more nuanced opinions, help to better understand the feedback and to identify areas for improvement. The various parties involved generally appreciate these tools. It should not be particularly difficult to collect and analyze these results. Nevertheless, different patients will enrolled during the observational and interventional phases. Consequently, the differences in satisfaction, if any, may also be due to a difference in individuals between the two groups. A low response rate from professionals to the satisfaction survey is expected, as described in the literature (65).

This study involves only one hospital and focuses on one type of implantation. This is a preliminary study before scaling up a larger, multi-center and randomized trial with several implantable medical devices (IMDs). This future study will follow a stepped-wedge method consisting of randomization by center and not by patient for the deployment of before-and-after phases in each of the participating centers. This study is a major step towards evaluating the efficacy of clinical pharmacy applied to IMDs with the aim of a larger-scale study with valuable randomization. At this moment, the before-after design appears to be the closest to the stepped-wedge method since they share separate observational and interventional periods. Indeed, randomization is not possible given the nature of the intervention and the high risk of contamination bias. This point is critical. Moreover, the measurement and analysis of costs is limited to direct hospital medical costs, which does not allow an overall analysis of the costs of care. Additional health economics analyses are planned for the multicenter study.

This study will investigate the impact of the integration of clinical pharmacy activities during the overall care pathway. This is the first step towards a change in practices, improved communication between professionals, better collaboration and the integration of a clinical pharmacist into multidisciplinary teams, including surgical ones. This study is the first, to our knowledge, to focus on clinical pharmacy for implantable MDs with a hard, clinical endpoint.

Potential limitations and bias

Since the study is not randomized, the selection bias and two non-comparable samples are risky. To overcome this limitation, an adjustment on the main confounding factors (such as age, sex and comorbidity index) will be considered.

Blinding is not possible due to the nature of the intervention. To limit a measurement bias, a blind methodologist will analyze the primary endpoint.

Recruitment may take longer than expected because all the PICC lines are placed in the operating room and are not a priority as opposed to life-threatening emergencies.

Phone calls to collect clinical data on complications, deaths and rehospitalizations are limited. The collected data is based solely on the patients' and care providers' statements. It is possible that they may intentionally or unintentionally omit some information. The plurality of involved counterparts may help to corroborate the given information. Data collection will be harmonized by double-checking the collection forms and the information collected at the time of the pharmaceutical interviews and phone calls.

Trial status

National registration number: 2019-A02475-52

Clinical Trials registration number: NCT04359056

Abbreviations

ENEIS: Enquête nationale sur les évènements indésirables graves associés aux soins (National French Adverse Events Study)

HAS: Haute Autorité de Santé (French National Authority for Health)

Figure legends

Figure 1: Study design.

Authors' statement

Alix Marie POUGET, Elodie CIVADE and Charlotte ROUZAUD-LABORDE contributed to the conception of the study. The authors will be responsible for the acquisition and analysis of the data, interpretation and dissemination of the results.

Alix Marie POUGET and Charlotte ROUZAUD-LABORDE contributed to the draft of this protocol.

Alix Marie POUGET, Elodie CIVADE, Philippe CESTAC and Charlotte ROUZAUD-LABORDE contributed to the revision of this protocol and approved the final version to be published.

All authors have agreed to be accountable for all aspects of the study such as accuracy and integrity of the work.

Author's declarations

There is no personal data in the protocol.

Additional data and materials are not available except through the corresponding author.

The authors do not declare any conflict of interest.

Sponsor

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Ethics and dissemination

The regional French Ethics Committee (CPP South-East VI, Clermont-Ferrand, France) assessed the scientific ethics of the protocol (version dated 3 February 2020) and approved this study.

All data collected will be anonymized and access to the data will be restricted to those participating in the research (investigators, pharmacists and pharmacy residents).

The results of the study will be published when available.

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References

1. Société Française de Pharmacie Clinique (SFPC). Présentation de la Pharmacie Clinique [Internet]. 2016. Available from: http://sfpc.eu/fr/la-sfpc/presentation.html
2. Jack BW, Chetty VK, Anthony D, Greenwald JL, Sanchez GM, Johnson AE, et al. A Reengineered Hospital Discharge Program to Decrease Rehospitalization: A Randomized Trial [Internet]. 2009 [cited 2019 Dec 2]. Available from: www.annals.org.
3. Pal A, Babbott S, Wilkinson ST. Can the targeted use of a discharge pharmacist significantly decrease 30-day readmissions? Hosp Pharm. 2013 May 1;48(5):380–8.
4. McKay C, Park C, Chang J, Brackbill M, Choi JY, Lee JH, et al. Systematic Review and Meta-analysis of Pharmacist-Led Transitions of Care Services on the 30-Day All-Cause Readmission Rate of Patients with Congestive Heart Failure. Vol. 39, Clinical Drug Investigation. Springer International Publishing; 2019. p. 703–12.
5. Renaudin P, Boyer L, Esteve M-A, Bertault-Peres P, Auquier P, Honore S. Do pharmacist-led medication reviews in hospitals help reduce hospital readmissions? A systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82(6):1660–73.
6. Haute Autorité de Santé - Mettre en œuvre la conciliation des traitements médicamenteux en établissement de santé [Internet]. [cited 2019 Dec 2]. Available from: https://www.has-sante.fr/jcms/c_2736453/fr/mettre-en-oeuvre-la-conciliation-des-traitements-medicamenteux-en-etablissement-de-sante
7. Lipton HL, Bird JA. The Impact of Clinical Pharmacists' Consultations on Geriatric Patients' Compliance and Medical Care Use: A Randomized Controlled Trial. Gerontologist. 2011;34(3):307–15.
8. Sadik A, Yousif M, McElnay JC. Pharmaceutical care of patients with heart failure. Br J Clin Pharmacol. 2005;60(2):183–93.
9. Leguelinel-Blache G, Arnaud F, Bouvet S, Dubois F, Castelli C, Roux-Marson C, et al. Impact of

admission medication reconciliation performed by clinical pharmacists on medication safety. Eur J Intern Med [Internet]. 2014;25(9):808–14. Available from: http://dx.doi.org/10.1016/j.ejim.2014.09.012

10. Lehnbom EC, Stewart MJ, Manias E, Westbrook JI. Impact of Medication Reconciliation and Review on Clinical Outcomes. Ann Pharmacother. 2014;48(10):1298–312.
11. Mekonnen AB, McLachlan AJ, Brien JAE. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: A systematic review and meta-analysis. Vol. 6, BMJ Open. BMJ Publishing Group; 2016.
12. Daliri S, Hugtenburg JG, Ter Riet G, Van den Bemt BJF, Buurman BM, Scholte op Reimer WJM, et al. The effect of a pharmacy-led transitional care program on medication-related problems post-discharge: A before—After prospective study. PLoS One. 2019 Mar 1;14(3).
13. Ferrand E, Painchart L, Grimandi G, Décaudin B, Bussières J. Rôles et retombées des pharmaciens dans la gestion des dispositifs médicaux en établissement de santé : une revue de littérature. Ann Pharm Fr [Internet]. 2017; Available from: http://dx.doi.org/10.1016/j.pharma.2017.05.001
14. Painchart L, Drancourt P, Aubert J, Inghels Y, Boyer J. Interest and difficulties in setting up pharmaceutical reconciliations for patients with dressings for complex wounds. Ann Pharm Fr. 2019;
15. Kumar A, Kethireddy S, Darovic GO. Catheter-related and infusion-related sepsis. Vol. 29, Critical Care Clinics. Crit Care Clin; 2013. p. 989–1015.
16. Rupp ME, Karnatak R. Intravascular Catheter–Related Bloodstream Infections. Vol. 32, Infectious Disease Clinics of North America. W.B. Saunders; 2018. p. 765–87.
17. Lee JH, Kim ET, Shim DJ, Kim IJ, Byeon JH, Lee IJ, et al. Prevalence and predictors of peripherally inserted central catheter-associated bloodstream infections in adults: A multicenter cohort study. PLoS One. 2019;14(3).
18. Bartock L. An Evidence-Based Systematic Review of Literature for the Reduction of PICC Line

Occlusions. J Assoc Vasc Access [Internet]. 2010;15(2):58–63. Available from: http://dx.doi.org/10.2309/java.15-2-3

19. Grove JR, Pevec WC. Venous thrombosis related to peripherally inserted central catheters. J Vasc Interv Radiol. 2000;11(7):837–40.

20. Cowl CT, Weinstock J V., Al-Jurf A, Ephgrave K, Murray JA, Dillon K. Complications and cost associated with parenteral nutrition delivered to hospitalized patients through either subclavian or peripherally-inserted central catheters. Clin Nutr. 2000;19(4):237–43.

21. Amerasekera SSH, Jones CM, Patel R, Cleasby MJ. Imaging of the complications of peripherally inserted central venous catheters. Clin Radiol [Internet]. 2009;64(8):832–40. Available from: http://dx.doi.org/10.1016/j.crad.2009.02.021

22. Leroyer C, Lashéras A, Marie V, Le Bras Y, Carteret T, Dupon M, et al. Prospective follow-up of complications related to peripherally inserted central catheters. Med Mal Infect [Internet]. 2013;43(8):350–5. Available from: http://dx.doi.org/10.1016/j.medmal.2013.06.013

23. Greene MT, Flanders SA, Woller SC, Bernstein SJ, Chopra V. The Association between PICC Use and Venous Thromboembolism in Upper and Lower Extremities. Am J Med. 2015;128(9).

24. Bertoglio S, Faccini B, Lalli L, Cafiero F, Bruzzi P. Peripherally inserted central catheters (PICCs) in cancer patients under chemotherapy: A prospective study on the incidence of complications and overall failures. J Surg Oncol. 2016;113(6).

25. Jones D, Wismayer K, Bozas G, Palmer J, Elliott M, Maraveyas A. The risk of venous thromboembolism associated with peripherally inserted central catheters in ambulant cancer patients. Thromb J. 2017;15(1):1–6.

26. Grau D, Clarivet B, Lotthé A, Bommart S, Parer S. Complications with peripherally inserted central catheters (PICCs) used in hospitalized patients and outpatients: A prospective cohort study. Antimicrob Resist Infect Control [Internet]. 2017;6(1):1–8. Available from: http://dx.doi.org/10.1186/s13756-016-0161-0

27. Opilla M. Peripherally Inserted Central Catheter Experience in Long-Term Home Parenteral

Nutrition Patients. JAVA - J Assoc Vasc Access [Internet]. 2017;22(1):42–5. Available from: http://dx.doi.org/10.1016/j.java.2016.12.001

28. Société Française d'Hygiène Hospitalière (SF2H). Bonnes Pratiques Et Gestion Des Risques Associés Au Picc -Hygiènes -Volume Xxi -N° 6. 2013; Available from: https://sf2h.net/wp-content/uploads/2014/05/SF2H_bonnes-pratiques-et-gestion-des-risques-associes-au-PICC-2013.pdf

29. Gallagher J, McCarthy S, Byrne S. Economic evaluations of clinical pharmacist interventions on hospital inpatients: a systematic review of recent literature. Int J Clin Pharm. 2014;36(6):1101–14.

30. Lawson EH, Hall BL, Louie R, Ettner SL, Zingmond DS, Han L, et al. Association between occurrence of a postoperative complication and readmission: Implications for quality improvement and cost savings. Ann Surg. 2013;258(1):10–8.

31. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: Defining standard protocol items for clinical trials. Vol. 158, Annals of Internal Medicine. American College of Physicians; 2013. p. 200–7.

32. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;

33. Dale A, Copeland R, Barton R. Prescribing errors on medical wards and the impact of clinical pharmacists. Int J Pharm Pract. 2005;11(1):19–24.

34. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72–83.

35. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol [Internet]. 2015 Jul 14 [cited 2020 Feb 24];71(7):861–75. Available from: http://link.springer.com/10.1007/s00228-015-1860-9

36. Haygood TM, Malhotra K, Ng C, Chasen B, McEnery KW, Chasen M. Migration of central lines from the superior vena cava to the azygous vein. Clin Radiol. 2012;67(1):49–54.

37. Moureau N. Impact and Safety Associated with Accidental Dislodgement of Vascular Access Devices: A Survey of Professions, Settings, and Devices. JAVA - J Assoc Vasc Access [Internet]. 2018;23(4):203–15. Available from: https://doi.org/10.1016/j.java.2018.07.002

38. Chopra V, Anand S, Krein SL, Chenoweth C, Saint S. Bloodstream infection, venous thrombosis, and peripherally inserted central catheters: Reappraising the evidence. Am J Med [Internet]. 2012;125(8):733–41. Available from: http://dx.doi.org/10.1016/j.amjmed.2012.04.010

39. Fallouh N, McGuirk HM, Flanders SA, Chopra V. Peripherally inserted central catheter-associated deep vein thrombosis: A narrative review. Am J Med. 2015;128(7).

40. Unplanned hospital visits [Internet]. [cited 2019 Dec 23]. Available from: https://www.medicare.gov/hospitalcompare/Data/Hospital-returns.html

41. Koehler BE, Richter KM, Youngblood L, Cohen BA, Prengler ID, Cheng D, et al. Reduction of 30-day postdischarge hospital readmission or emergency department (ED) visit rates in high-risk elderly medical patients through delivery of a targeted care bundle. J Hosp Med. 2009;4(4):211–8.

42. Hohl CM, Partovi N, Ghement I, Wickham ME, McGrail K, Reddekopp LN, et al. Impact of early in-hospital medication review by clinical pharmacists on health services utilization. PLoS One. 2017;12(2):1–13.

43. Bedouch P, Charpiat B, Conort O, Rose FX, Escofier L, Juste M, et al. Assessment of clinical pharmacists' interventions in French Hospitals: Results of a multicenter study. Ann Pharmacother. 2008 Jul;42(7–8):1095–103.

44. Charpiat B, Bedouch P, Conort O, Rose FX, Juste M, Roubille R, et al. Opportunités d'erreurs médicamenteuses et interventions pharmaceutiques dans le cadre de la prescription informatisée : Revue des données publiées par les pharmaciens hospitaliers français. Vol. 70, Annales Pharmaceutiques Francaises. 2012. p. 62–74.

45. Charpiat B, Conort O, Juste M, Rose FX, Roubille R, Bedouch P, et al. Mise à disposition de l'outil de codification des interventions pharmaceutiques de la Société française de pharmacie clinique : bilan à 10 ans et perspectives. Vol. 50, Pharmacien Hospitalier et Clinicien. Elsevier Masson SAS; 2015. p. e15–24.

46. Mongaret C, Quillet P, Vo TH, Aubert L, Fourgeaud M, Michelet-Huot E, et al. Predictive factors for clinically significant pharmacist interventions at hospital admission. Vol. 97, Medicine (United States). Lippincott Williams and Wilkins; 2018.

47. Aguiar K da S, Santos JM Dos, Cambrussi MC, Picolotto S, Carneiro MB. Patient safety and the value of pharmaceutical intervention in a cancer hospital. Einstein (Sao Paulo). 2018;16(1):eAO4122.

48. Ha Vo T. Evaluation of the potential impact of pharmacist interventions : development and validation of the CLEO multidimensional tool [Internet]. [cited 2020 Feb 24]. Available from: https://tel.archives-ouvertes.fr/tel-01315619

49. Moons K, Waeyenbergh G, Pintelon L. Measuring the logistics performance of internal hospital supply chains – A literature study. Omega (United Kingdom) [Internet]. 2019;82:205–17. Available from: https://doi.org/10.1016/j.omega.2018.01.007

50. Chasseigne V, Leguelinel-Blache G, Nguyen TL, de Tayrac R, Prudhomme M, Kinowski JM, et al. Assessing the costs of disposable and reusable supplies wasted during surgeries. Int J Surg [Internet]. 2018;53:18–23. Available from: https://doi.org/10.1016/j.ijsu.2018.02.004

51. Société Française d'Hygiène Hospitalière (SF2H). Good practice and risk management for the use of PICC. 2013;(December).

52. Redmond P, Grimes TC, Mcdonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. Vol. 2018, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2018.

53. Andrade LF, Ludwig K, Goni JMR, Oppe M, de Pouvourville G. A French Value Set for the EQ-5D-5L. Pharmacoeconomics [Internet]. 2020;38(4):413–25. Available from:

https://doi.org/10.1007/s40273-019-00876-4

54. Chasseigne V, Bouvet S, Chkair S, Buisson M, Richard M, de Tayrac R, et al. Health economic evaluation of a clinical pharmacist's intervention on the appropriate use of devices and cost savings: A pilot study. Int J Surg. 2020;82(July):143–8.

55. Michel P, Lathelize M, Bru-Sonnet R, Perez C, Domecq S, Kret M, et al. Rapport final - Comparaison des deux études ENEIS 2004 et 2009. Drees, Ministère la santé. 2011;1–118.

56. Christensen LD, Holst M, Bech LF, Drustrup L, Nygaard L, Skallerup A, et al. Comparison of complications associated with peripherally inserted central catheters and Hickman™ catheters in patients with intestinal failure receiving home parenteral nutrition. Six-year follow up study. Clin Nutr [Internet]. 2016;35(4):912–7. Available from: http://dx.doi.org/10.1016/j.clnu.2015.06.009

57. Santacruz E, Mateo-Lobo R, Riveiro J, Nattero L, Vega-Piñero B, Lomba G, et al. Infectious complications in home parenteral nutrition: A long-term study with peripherally inserted central catheters, tunneled catheters, and ports. Nutrition. 2019;58:89–93.

58. Kilcup M, Schultz D, Carlson J, Wilson B. Postdischarge pharmacist medication reconciliation: Impact on readmission rates and financial savings. J Am Pharm Assoc. 2013;53(1):78–84.

59. Jones CD, Anthony A, Klein MD, Shakowski C, Smith HK, Go A, et al. The effect of a pharmacist-led multidisciplinary transitions-of-care pilot for patients at high risk of readmission. J Am Pharm Assoc. 2018 Sep 1;58(5):554–60.

60. Lussier ME, Evans HJ, Wright EA, Gionfriddo MR. The impact of community pharmacist involvement on transitions of care: A systematic review and meta-analysis. J Am Pharm Assoc [Internet]. 2019; Available from: https://doi.org/10.1016/j.japh.2019.07.002

61. Leguelinel-Blache G, Castelli C, Roux-Marson C, Bouvet S, Andrieu S, Cestac P, et al. Impact of collaborative pharmaceutical care on in-patients' medication safety: Study protocol for a stepped wedge cluster randomized trial (MEDREV study). Trials. 2018 Jan 8;19(1).

62. Ensing HT, Stuijt CCM, Van Den Bemt BJF, Van Dooren AA, Karapinar-Çarkit F, Koster ES, et al.

Identifying the optimal role for pharmacists in care transitions: A systematic review. Vol. 21, Journal of Managed Care Pharmacy. Academy of Managed Care Pharmacy (AMCP); 2015. p. 614–38.

63. Rigby K. Adverse events in health care: Setting priorities based on economic evaluation. J Qual Clin Pract. 1999;19(1):7–12.

64. Likert R. A technique for the measurement of attitudes. Arch Psychol. 1932;22(140):55.

65. Cook J V., Dickinson HO, Eccles MP. Response rates in postal surveys of healthcare professionals between 1996 and 2005: An observational study. BMC Health Serv Res. 2009;9:1–8.

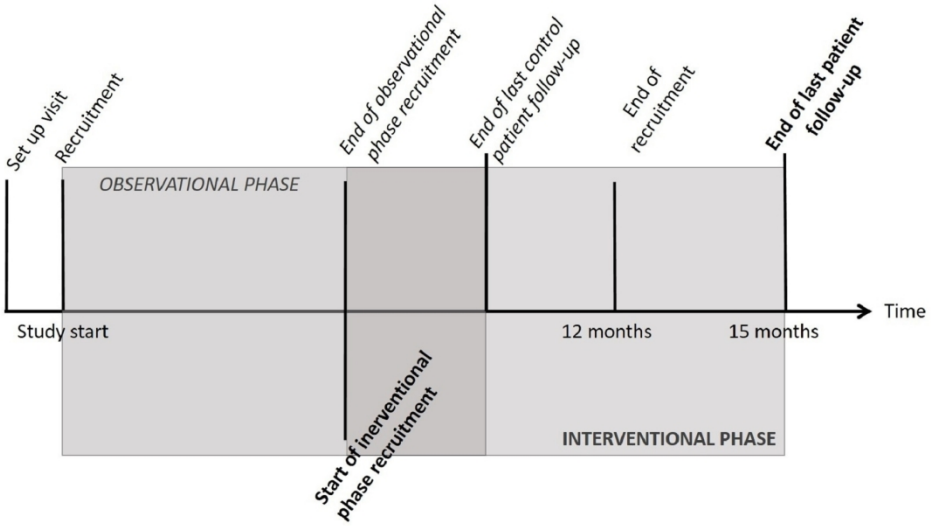

Figure 1: Study design.

159x91mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 15
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data	16

		management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3, 4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4,5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5,6,7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7,8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9,10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, 7-8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4,5
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4, 14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	blinding is not possible in this study except for analysis

Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13,14

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10,11,12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10,11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods:			
Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	before-after study: interim analysis not necessary

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5-8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A, no ancillary studies planned

Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A , no ancillary trials.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16, all supplementary data through corresponding author
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	4, model as supplementary files
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A, no biological specimens

Notes:

- 11a: 8, 9, 10, 11, 12
- 17b: blinding is not possible in this study exept for analysis
- 21b: before-after study: interim analysis not necessary
- 26b: N/A, no ancillary studies planned
- 30: N/A , no ancillary trials.
- 31c: 24, all supplementary data through corresponding author
- 32: documents approuved by the ethic committee (24)

- 33: N/A, no biological specimens This checklist was completed on 07. April 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

From hospitalization to primary care, integrative model of clinical pharmacy with patients implanted with a PICC line: research protocol for a prospective before-after study.

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Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Health services research, Patient-centred medicine
Keywords:	CLINICAL PHARMACOLOGY, Clinical trials < THERAPEUTICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

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From hospitalization to primary care, integrative model of clinical pharmacy with patients implanted with a PICC line: research protocol for a prospective before-after study

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Trial acronym: CLIPICC

Abstract

Introduction

Clinical pharmacy improves patient safety and secures drug management using information, education and good clinical practices. However, medical device management is still unexplored, and proof of effectiveness is needed. A PICC line is a medical device for infusion. It accesses the central venous system after being implanted in a peripheral vein. But complications after implantation often interfere with smooth execution of the treatment. We hypothesize that clinical pharmacy for medical devices could be as effective as clinical pharmacy for medications. The main objective is to assess the effectiveness of clinical pharmacy activities on the complication rate after PICC line implantation.

Methods and analysis

This is a before-after prospective study. The study will begin with an observational period without clinical pharmacy activities, followed by an interventional period where pharmacists will intervene on drug and medical device management and provide personalized follow-up and advice. Sixty-nine adult patients will be recruited in each 6-month period from all traditional care units. The main inclusion criteria will be the implantation of a PICC line. The primary outcome is the decrease in the number of complications per patient and per month. Secondary outcomes are the consultation and hospital readmission rates, the acceptance rate of pharmaceutical interventions, the patients' quality of life, the direct hospital induced or avoided costs and the participants' satisfaction. Data will be collected using Case Report Forms during hospitalization and telephone follow-up after discharge. The analysis will compare these criteria during the two periods.

Ethics and dissemination

The study has received the approval of our Ethics Committee (Clermont-Ferrand Southeast VI, France, number AU1586). Results will be made available to the patients or their caregivers, the sponsor and other researchers when asked, as described in the consent form.

Trial registration

2019-A02475-52 (ID-RCB number)
ClinicalTrials.gov*:* NCT04359056

Keywords

Clinical Pharmacy, Medical Devices, PICC lines, Protocol, Before-After Study

Strengths and Limitations

- This is the first study to assess the effectiveness of clinical pharmacy interventions for medical devices.
- As a primary objective, strong clinical criteria will be evaluated by measuring skin redness or fever (as signs of an infection), edema, thrombosis and pain.
- This study proposes an integrative model of clinical pharmacy, from hospitalization to primary care.
- The main limitations of this study are the lack of randomization and the lack of blinding for patients and healthcare professionals.

Introduction

Clinical pharmacy is a patient-centered health discipline whose practice aims to optimize therapy at each stage of the care pathway. Clinical pharmacy actions contribute to patient safety and the relevant and efficient use of health products (1). To ensure health products are used in a safe and appropriate manner, pharmacists analyze physicians' orders to identify errors or potentially inappropriate prescriptions based on guidelines and evidence-based medicine. Moreover, they optimize drug intake, inform patients and caregivers, organize the discharge to primary care and disseminate clinical good practices. Pharmacists also focus on patient education, information, and training for healthcare professionals.

Regarding medication approaches, the effectiveness of clinical pharmacy is well known. Several clinical studies have demonstrated significant impacts on re-hospitalizations (2–5), drug management (6) and treatment compliance (7), patients' quality of life(8) as well as a decrease of iatrogenic risk (9–12). But studies on clinical pharmacy in the context of medical devices (MD) are rare (13). To our knowledge, no study has described the clinical impact of a pharmacist's intervention when a MD is implanted in patients. Only one recent article refers to clinical pharmacy in dressings for complex wounds (14). The need for further clinical studies is undeniable.

MD classification is based on their risk of invasiveness and duration of use. Infusion equipment, such as catheters, can induce iatrogenic events, especially infections (15,16). Peripherally inserted central catheters (PICC lines) are associated with numerous clinical (e.g. infections (17)) and mechanical complications (e. g. catheter occlusions (18)) (19–27). PICC lines are useful for the administration of irritating products or for the repeated collection of blood samples. PICC lines are recommended when the duration of catheterization ranges from 7 days to 3 months (28). PICC line implantations are carried out in the interventional radiology operating room.

Our working hypothesis is that clinical pharmacy interventions will prevent clinical and mechanical complications and thereby reduce hospital costs(29). Reducing complications could also prevent its consequences such as rehospitalizations (30) and physician visits.

Methods and Analysis

A scientific committee (selected by the Research and Innovation Board of the Toulouse University Hospital) composed of scientific and methodological experts and statisticians oversaw the feasibility and methodology of the study. This committee ensures the quality and relevance of the research organization. The study procedures and assessments comply with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials (31)) checklist.

Design

A pragmatic single center design is used. This is a before-after prospective study with two consecutive phases: observational (no clinical pharmacy activities) and interventional (execution of clinical pharmacy activities and logistics optimization). Randomization of patients is not possible in this study due to the high risk of contamination bias. Once the clinical pharmacist arrives in the care unit, he or she should address any medical apprehension by the PICC prescribers and nurses, explaining good clinical use, affecting all the future study patients, even the control group. This is an open study. Due to the nature of the pharmaceutical interventions, blinding is not possible for patients and care providers.

Setting

The study will take place in the Toulouse University Hospital Center. Every PICC line prescription will be picked up in the interventional radiology unit and patients will be screened for eligibility. Patients will be recruited from their hospital ward prior to the PICC line insertion. All selected participants will be asked to read and sign a consent form (supplementary file). Each phase (observational and

interventional) will last approximately 9 months taking into account recruitment and patient follow-up. See Figure 1 for the study timeline.

Recruitment began on Monday, May 25, 2020 and will end 1 year later on May 25, 2021. The study is scheduled to end on August 25, 2021.

Characteristics of participants: Inclusion and exclusion criteria

Eligibility criteria are listed in Table 1. For all included patients, the Charlson Comorbidity Index (32) will be use to assess the degree of comorbidity at baseline.

Inclusion criteria	Adult patient, 18 years of age or older Patient capable of giving free and informed consent Patient insured by the Social Security System in France Patient living at home Patient with a PICC line prescription Patient whose discharge prescription should contain drugs and MDs Patient for home discharge implanted with a PICC line Patient reachable by phone
Exclusion criteria	Under-aged patient, less than 18 years old Patient not insurance by the Social Security System in France Patient not living at home: Institutionalized patient Patient living in a facility for elderly dependent persons Nursing home resident “Hospital at Home” patient Patient deprived of their freedom by a judicial or administrative decision Patient under guardianship, curatorship or safeguard of justice Patient unreachable by phone Pregnant or breastfeeding women

Table 1 : Inclusion and exclusion criteria

Patient and public involvement

No patient involved.

Process

Regardless of the phase of the study, the occurrence of complications due to the PICC line will be recorded during hospitalization and at home during a follow-up phone call. Patients are monitored for the entire duration of the PICC line implantation or for a maximum of 3 months. Data will be collected at days 3 and 7 (D3 or D7 respectively) after implantation and then after 1, 2 and 3 months (M1, M2 and M3 respectively).

The control period corresponds to usual care and represents the observational phase, where no pharmaceutic interventions will be done, unless necessary for the patient's safety (e.g. life-threatening situations(33)).

One participant can be included in only one phase. The interventional phase will start when the last patient is included in the observational phase. Physicians and nurses, as well as other healthcare professionals, will attend training sessions on updates, recommendations, indications, and maintenance related the use of PICC lines. If necessary, training sessions will be repeated once to make sure the research team met all the healthcare professionals involved.

Two pharmacists and a pharmacy resident will participate in each phase.

The following table (Table 2) describes the research procedures and activities in the two phases.

Timepoint	*Research steps*	Observational phase	Interventional phase
HOSPITALIZATION	***PICC line prescription***	Screening: Eligibility assessment	
	Intervention scheduled	Enrollment: Informed consent	
	PICC line indication	Document purpose and duration of catheterization	
			Pharmaceutical analysis to identify errors or potentially inappropriate prescriptions[1]; discussion with prescribers; pharmaceutical interventions in the event of unjustified deviation from existing guidelines
	In the operating room (OR) before the implantation	Verify that all necessary equipment is available for the surgery	
			Help with ordering if necessary
		Conformity assessment of the expiration date for all PICC lines stored in the OR's supply room	
			Help with ordering if necessary. Rationalization of the medical device stock if necessary
		Conformity assessment of traceability from receipt of the medical device order by the pharmacy to delivery to the care unit	
			Corrections if necessary
	Implantation of PICC line = day 0	Number of medical devices used during the operation (implantation failures or non-functional devices)	
		Implantation traceability to ensure lot numbers match in the patient's record, the OR book and the computer software	
			Corrections if necessary
	Remainder of the hospitalization	Record possible complications during the remainder of the hospital stay	
			Corrections and help if complications occur
DISCHARGE	***Discharge prescription***	Pharmaceutical analysis of the patient's discharge order. The analysis will focus on drugs and MDs related to the PICC line (e.g. dressing repair set). Conformity analysis of the hospital prescriptions issued by local pharmacy	
			Pharmaceutical analysis of the patient's discharge order and optimization[1] if necessary. Discussion with the physician and correction
	Patient discharge	Quality of Life assessment (EQ5D5L scale)	
			Pharmaceutical interview with the patient:

			Discuss the different treatments on the discharge order, answer any questions. Provide information about the PICC line, how to use it, maintain it and how to detect potential complications. Make sure that traceability documents are provided. Make sure that the PICC line's user booklet is provided. Transmission of the discharge order to the community pharmacist.
PRIMARY CARE	***Day 3*** ***Day 7***	Phone calls to collect complications or any events regarding the PICC line and drugs -Patient -Private nurse	
			Provide personalized and appropriate advice Pharmaceutical interventions if necessary
	M1, M2	Phone calls to collect complications or any events regarding the PICC line and drugs: -Patient -Private nurse Phone calls to community pharmacist to record information related to care consumption	
			Provide personalized and appropriate advice Pharmaceutical interventions if necessary
	M3	Quality of Life assessment (EQ5D5L scale) Phone calls to collect complications or any events regarding the PICC line and drugs: -Patient -Private nurse -Community pharmacist to record information related to care consumption -General practitioner to identify any consultations related to the PICC line and any other relevant information Sooner if there is a need to confirm clinical data on complications such as thrombotic events.	

Table 2: Detailed research process. [1]According to the gold standard or START and STOPP method(34) *or European PIM list*(35) *for older adults*

At the end of the study, a satisfaction survey will be sent to every participant (patients and caregivers).

Outcomes and expected benefits

Primary outcome

The primary outcome is the number of complications per patient and per month. Complications will be documented on specific forms to harmonize data collection. Mechanical complications are defined as obstruction or occlusion (18), breakage or damage to the catheter(27), migration (36), or dislodgment (accidental withdrawal) of the catheter(37). Clinical complications are defined as redness around the insertion site (diameter > 2 cm), edema (size difference between the two hands), pain (numeric rating scale), fever (internal temperature > 37°C) as signs of an infection(17,38) and thrombotic events(39) (confirmed by a medical modality such as echography).

Secondary outcomes

The number of consultations and rehospitalizations post-discharge will be used to determine the clinical impact beyond the initial hospitalization (11,40–42). The expected result is a decrease in the consultation and rehospitalization rates at the end of the intervention phase compared to the observation phase.

The acceptance rate of pharmaceutical interventions during the interventional phase is used to assess the appropriateness of pharmaceutical interventions (43–47). A higher acceptance rate means the pharmaceutical interventions are justified and relevant to the care providers. The criticality of the pharmacist's intervention (48) will be evaluated. Moreover, conformity of the hospital prescriptions for primary care after the discharge will be assessed. The aim is to avoid treatment breaks.

Another secondary outcome involves the conformity analysis of the PICC line logistics circuit (checklist related to stock, supply chain, traceability). Management of the hospital supply chain is a major financial challenge (49) and generally leads to decreased treatment risk and costs (50). The objective is to streamline the various stages of the PICC line logistics circuit, from ordering to implantation. By streamlining the logistics, improved patient safety and reduced costs are expected.

The conformity of the PICC line indication will be evaluated according to recommendations(51). Prescriptions too often seem to be trivialized and little guided by attending doctors. Therefore, errors are possible. The aim is to improve the team's knowledge and the communication between hospital units.

The patients' quality of life before and after the follow-up will be measured with the EQ5D5Lquestionnaire (52). As previously described by Andrade et al. (53), a standard value set for converting the profiles on the 5 dimensions onto a score will be used.

An improvement in the quality of life score is expected during the intervention phase.

Satisfaction of the patients and the healthcare providers involved will be evaluated. To develop clinical pharmacy activities in health care services, collaboration and communication with health care teams is essential.

The direct hospital costs will be estimated and described. The objective is to estimate whether additional costs are induced, or whether costs are spared through better organization and logistics management (54).

Statistical analysis

Sample Size Calculation

According to the ENEIS studies (2004 and 2009) and their final report (55), at least 50% of iatrogenic serious adverse events are preventable whether due to medications or MDs. Assuming that clinical pharmacy integration could theoretically lead to a 25% decrease in the complication rate during the interventional phase, 62 patients are needed in each group (80% power, alpha 5%). Thus, 138 patients need to be recruited assuming that 10% are lost to follow-up. All early exits from the study will be considered as lost to follow-up and the affected data will be processed in the statistical analysis as intent-to-treat.

Statistics

Statistical tests will be used that are appropriate for the distribution of the variables. All tests will be performed at an alpha risk of 5%. Categorical variables will be described by counts and percentages. Means and standard deviations will be reported for continuous variables with normal distribution, and median and quartiles for other continuous variables.

Patient demographics and clinical characteristics will be described.

To assess the effectiveness of the intervention, means or medians of the number of complications per month and per patient for each phase will be estimated and a Poisson regression will be used. An adjustment for confounding factors such as sex, age and Charlson Comorbidity Index is planned.

The secondary outcomes will be analyzed as described in Table 3.

Table 3 : Statistical analysis for the secondary outcomes

Variables types	Variables of interest	Description*	Tests*
Quantitative	• Consultations and rehospitalizations after discharge • EQ5D5L scores • Direct hospital costs	Means ± Standard Deviation (SD) or Medians and quartiles Frequency table	Student's *t* test or non-parametric Wilcoxon's test
Qualitative	• Conformity rates (logistics, indications for implantation and prescriptions issued by local pharmacy) • Satisfaction levels	Frequency table	Chi^2 test or Fisher's exact test

*According to the distribution of variables.

Discussion

The main objective is to demonstrate the effectiveness of clinical pharmacy activities in preventing complications in patients implanted with a PICC line. This is a strong clinical criterion. There is abundant literature about the occurrence of complications following the insertion of a PICC line, in a hospital (20–24) or at home(27,56,57). At the same time, reported rates vary widely across studies. These rates

were pooled to estimate an "average" complication rate. This method was used to calculate the number of subjects needed for this study. These assumptions have an impact on the robustness of the study and may require the use of statistical adjustments when analyzing the results. As for complications, the numbers of consultations and rehospitalizations post-discharge have been used in several studies, particularly the 30-day readmission rate (11,42,58–60) to assess the clinical effectiveness of a pharmacist's interventions. Despite the wide assortment of these rates in the literature, this indicator is relevant for comparing our study to others. However, it will be difficult to obtain exhaustive results, as the data will be derived from statements made by the different participants. The information will only be formally verifiable if the patient in question is readmitted or consults in one of our hospital's departments.

The acceptance rate of pharmaceutical interventions is not only a widely used and recognized indicator (43,61) for assessing the appropriateness of interventions, it is also an indicator routinely used in hospitals. A conformity analysis of the hospital prescriptions for primary care is one of the secondary endpoints. It seems essential to secure these prescriptions also because the patient's transition is known to be a high risk event (62). Good clinical practices allow health professionals to decrease errors and avoid potential errors in prescription. Iatrogenic events are associated with additional costs (63).

A checklist of items was developed to evaluate the conformity of the PICC line's logistics circuit. This list is particularly exhaustive and will be used by all those who collect data. This will avoid an evaluation bias that could be linked to the large number of healthcare providers involved. The checklist will help to identify the most common errors or pitfalls encountered and to establish adequate corrective measures. Current guidelines are available for the device's logistics (51).

The prospective study design allows to assess the patients' quality of life using the EQ-5D-5L Scale before and after the intervention. This criterion is needed to assess the patient's point of view, as the patient is the central element in the care pathway. To avoid interference or influence due to the presence of pharmacists, they will not to be present at the time of the first evaluation (day of discharge). However, the subsequent assessments will be done by telephone, thus pharmacists could

influence patient responses. Likert scales have been developed to collect patient and healthcare professional satisfaction data (64). These tools are valid and reliable for collecting the opinions of different research participants. These scales capture more nuanced opinions, help to better understand the feedback and to identify areas for improvement. The various parties involved generally appreciate these tools. It should not be particularly difficult to collect and analyze these results. Nevertheless, different patients will enrolled during the observational and interventional phases. Consequently, the differences in satisfaction, if any, may also be due to a difference in individuals between the two groups. A low response rate from professionals to the satisfaction survey is expected, as described in the literature (65).

This study involves only one hospital and focuses on one type of implantation. This is a preliminary study before scaling up a larger, multi-center and randomized trial with several implantable medical devices (IMDs). This future study will follow a stepped-wedge method consisting of randomization by center and not by patient for the deployment of before-and-after phases in each of the participating centers. This study is a major step towards evaluating the efficacy of clinical pharmacy applied to IMDs with the aim of a larger-scale study with valuable randomization. At this moment, the before-after design appears to be the closest to the stepped-wedge method since they share separate observational and interventional periods. Indeed, randomization is not possible given the nature of the intervention and the high risk of contamination bias. This point is critical. Moreover, the measurement and analysis of costs is limited to direct hospital medical costs, which does not allow an overall analysis of the costs of care. Additional health economics analyses are planned for the multicenter study.

This study will investigate the impact of the integration of clinical pharmacy activities during the overall care pathway. This is the first step towards a change in practices, improved communication between professionals, better collaboration and the integration of a clinical pharmacist into multidisciplinary teams, including surgical ones. This study is the first, to our knowledge, to focus on clinical pharmacy for implantable MDs with a hard, clinical endpoint.

Potential limitations and bias

Since the study is not randomized, the selection bias and two non-comparable samples are risky. To overcome this limitation, an adjustment on the main confounding factors (such as age, sex and comorbidity index) will be considered.

Blinding is not possible due to the nature of the intervention. To limit a measurement bias, a blind methodologist will analyze the primary endpoint.

Recruitment may take longer than expected because all the PICC lines are placed in the operating room and are not a priority as opposed to life-threatening emergencies.

Phone calls to collect clinical data on complications, deaths and rehospitalizations are limited. The collected data is based solely on the patients' and care providers' statements. It is possible that they may intentionally or unintentionally omit some information. The plurality of involved counterparts may help to corroborate the given information. Data collection will be harmonized by double-checking the collection forms and the information collected at the time of the pharmaceutical interviews and phone calls.

Trial status

Recruiting since May 25, 2020. On February 26, 50 volunteers have been enrolled in the study.

National registration number: 2019-A02475-52

Clinical Trials registration number: NCT04359056

Abbreviations

ENEIS: Enquête nationale sur les évènements indésirables graves associés aux soins (National French Adverse Events Study)

HAS: Haute Autorité de Santé (French National Authority for Health)

Figure legends

Figure 1: Study design.

Ethics and dissemination

The regional French Ethics Committee (CPP South-East VI, Clermont-Ferrand, France) assessed the scientific ethics of the protocol (version dated 3 February 2020) and approved this study.

All data collected will be anonymized and access to the data will be restricted to those participating in the research (investigators, pharmacists and pharmacy residents).

The results of the study will be published when available.

Authors' statement

Alix Marie POUGET, Elodie CIVADE and Charlotte ROUZAUD-LABORDE contributed to the conception of the study. The authors will be responsible for the acquisition and analysis of the data, interpretation and dissemination of the results.

Alix Marie POUGET and Charlotte ROUZAUD-LABORDE contributed to the draft of this protocol.

Alix Marie POUGET, Elodie CIVADE, Philippe CESTAC and Charlotte ROUZAUD-LABORDE contributed to the revision of this protocol and approved the final version to be published.

All authors have agreed to be accountable for all aspects of the study such as accuracy and integrity of the work.

Sponsor

The Research and Innovation Board of the Toulouse University Hospital Center is the sponsor of this study. The protocol is locally registered with the following number: RC31/18/0459.

Funding

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Data sharing statement

There is no personal data in the protocol.

Additional data and materials are not available except through the corresponding author.

Competing interests statement

The authors do not declare any conflict of interest.

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References

1. Société Française de Pharmacie Clinique (SFPC). Présentation de la Pharmacie Clinique [Internet]. 2016. Available from: http://sfpc.eu/fr/la-sfpc/presentation.html
2. Jack BW, Chetty VK, Anthony D, Greenwald JL, Sanchez GM, Johnson AE, et al. A Reengineered Hospital Discharge Program to Decrease Rehospitalization: A Randomized Trial [Internet]. 2009 [cited 2019 Dec 2]. Available from: www.annals.org.
3. Pal A, Babbott S, Wilkinson ST. Can the targeted use of a discharge pharmacist significantly decrease 30-day readmissions? Hosp Pharm. 2013 May 1;48(5):380–8.
4. McKay C, Park C, Chang J, Brackbill M, Choi JY, Lee JH, et al. Systematic Review and Meta-analysis of Pharmacist-Led Transitions of Care Services on the 30-Day All-Cause Readmission Rate of Patients with Congestive Heart Failure. Vol. 39, Clinical Drug Investigation. Springer International Publishing; 2019. p. 703–12.
5. Renaudin P, Boyer L, Esteve M-A, Bertault-Peres P, Auquier P, Honore S. Do pharmacist-led medication reviews in hospitals help reduce hospital readmissions? A systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82(6):1660–73.
6. Haute Autorité de Santé - Mettre en œuvre la conciliation des traitements médicamenteux en établissement de santé [Internet]. [cited 2019 Dec 2]. Available from: https://www.has-sante.fr/jcms/c_2736453/fr/mettre-en-oeuvre-la-conciliation-des-traitements-medicamenteux-en-etablissement-de-sante
7. Lipton HL, Bird JA. The Impact of Clinical Pharmacists' Consultations on Geriatric Patients' Compliance and Medical Care Use: A Randomized Controlled Trial. Gerontologist. 2011;34(3):307–15.
8. Sadik A, Yousif M, McElnay JC. Pharmaceutical care of patients with heart failure. Br J Clin Pharmacol. 2005;60(2):183–93.
9. Leguelinel-Blache G, Arnaud F, Bouvet S, Dubois F, Castelli C, Roux-Marson C, et al. Impact of

admission medication reconciliation performed by clinical pharmacists on medication safety. Eur J Intern Med [Internet]. 2014;25(9):808–14. Available from: http://dx.doi.org/10.1016/j.ejim.2014.09.012

10. Lehnbom EC, Stewart MJ, Manias E, Westbrook JI. Impact of Medication Reconciliation and Review on Clinical Outcomes. Ann Pharmacother. 2014;48(10):1298–312.
11. Mekonnen AB, McLachlan AJ, Brien JAE. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: A systematic review and meta-analysis. Vol. 6, BMJ Open. BMJ Publishing Group; 2016.
12. Daliri S, Hugtenburg JG, Ter Riet G, Van den Bemt BJF, Buurman BM, Scholte op Reimer WJM, et al. The effect of a pharmacy-led transitional care program on medication-related problems post-discharge: A before—After prospective study. PLoS One. 2019 Mar 1;14(3).
13. Ferrand E, Painchart L, Grimandi G, Décaudin B, Bussières J. Rôles et retombées des pharmaciens dans la gestion des dispositifs médicaux en établissement de santé : une revue de littérature. Ann Pharm Fr [Internet]. 2017; Available from: http://dx.doi.org/10.1016/j.pharma.2017.05.001
14. Painchart L, Drancourt P, Aubert J, Inghels Y, Boyer J. Interest and difficulties in setting up pharmaceutical reconciliations for patients with dressings for complex wounds. Ann Pharm Fr. 2019;
15. Kumar A, Kethireddy S, Darovic GO. Catheter-related and infusion-related sepsis. Vol. 29, Critical Care Clinics. Crit Care Clin; 2013. p. 989–1015.
16. Rupp ME, Karnatak R. Intravascular Catheter–Related Bloodstream Infections. Vol. 32, Infectious Disease Clinics of North America. W.B. Saunders; 2018. p. 765–87.
17. Lee JH, Kim ET, Shim DJ, Kim IJ, Byeon JH, Lee IJ, et al. Prevalence and predictors of peripherally inserted central catheter-associated bloodstream infections in adults: A multicenter cohort study. PLoS One. 2019;14(3).
18. Bartock L. An Evidence-Based Systematic Review of Literature for the Reduction of PICC Line

Occlusions. J Assoc Vasc Access [Internet]. 2010;15(2):58–63. Available from: http://dx.doi.org/10.2309/java.15-2-3

19. Grove JR, Pevec WC. Venous thrombosis related to peripherally inserted central catheters. J Vasc Interv Radiol. 2000;11(7):837–40.

20. Cowl CT, Weinstock J V., Al-Jurf A, Ephgrave K, Murray JA, Dillon K. Complications and cost associated with parenteral nutrition delivered to hospitalized patients through either subclavian or peripherally-inserted central catheters. Clin Nutr. 2000;19(4):237–43.

21. Amerasekera SSH, Jones CM, Patel R, Cleasby MJ. Imaging of the complications of peripherally inserted central venous catheters. Clin Radiol [Internet]. 2009;64(8):832–40. Available from: http://dx.doi.org/10.1016/j.crad.2009.02.021

22. Leroyer C, Lashéras A, Marie V, Le Bras Y, Carteret T, Dupon M, et al. Prospective follow-up of complications related to peripherally inserted central catheters. Med Mal Infect [Internet]. 2013;43(8):350–5. Available from: http://dx.doi.org/10.1016/j.medmal.2013.06.013

23. Greene MT, Flanders SA, Woller SC, Bernstein SJ, Chopra V. The Association between PICC Use and Venous Thromboembolism in Upper and Lower Extremities. Am J Med. 2015;128(9).

24. Bertoglio S, Faccini B, Lalli L, Cafiero F, Bruzzi P. Peripherally inserted central catheters (PICCs) in cancer patients under chemotherapy: A prospective study on the incidence of complications and overall failures. J Surg Oncol. 2016;113(6).

25. Jones D, Wismayer K, Bozas G, Palmer J, Elliott M, Maraveyas A. The risk of venous thromboembolism associated with peripherally inserted central catheters in ambulant cancer patients. Thromb J. 2017;15(1):1–6.

26. Grau D, Clarivet B, Lotthé A, Bommart S, Parer S. Complications with peripherally inserted central catheters (PICCs) used in hospitalized patients and outpatients: A prospective cohort study. Antimicrob Resist Infect Control [Internet]. 2017;6(1):1–8. Available from: http://dx.doi.org/10.1186/s13756-016-0161-0

27. Opilla M. Peripherally Inserted Central Catheter Experience in Long-Term Home Parenteral

Nutrition Patients. JAVA - J Assoc Vasc Access [Internet]. 2017;22(1):42–5. Available from: http://dx.doi.org/10.1016/j.java.2016.12.001

28. Société Française d'Hygiène Hospitalière (SF2H). Bonnes Pratiques Et Gestion Des Risques Associés Au Picc -Hygiènes -Volume Xxi -N° 6. 2013; Available from: https://sf2h.net/wp-content/uploads/2014/05/SF2H_bonnes-pratiques-et-gestion-des-risques-associes-au-PICC-2013.pdf

29. Gallagher J, McCarthy S, Byrne S. Economic evaluations of clinical pharmacist interventions on hospital inpatients: a systematic review of recent literature. Int J Clin Pharm. 2014;36(6):1101–14.

30. Lawson EH, Hall BL, Louie R, Ettner SL, Zingmond DS, Han L, et al. Association between occurrence of a postoperative complication and readmission: Implications for quality improvement and cost savings. Ann Surg. 2013;258(1):10–8.

31. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: Defining standard protocol items for clinical trials. Vol. 158, Annals of Internal Medicine. American College of Physicians; 2013. p. 200–7.

32. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;

33. Dale A, Copeland R, Barton R. Prescribing errors on medical wards and the impact of clinical pharmacists. Int J Pharm Pract. 2005;11(1):19–24.

34. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72–83.

35. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol [Internet]. 2015 Jul 14 [cited 2020 Feb 24];71(7):861–75. Available from: http://link.springer.com/10.1007/s00228-015-1860-9

36. Haygood TM, Malhotra K, Ng C, Chasen B, McEnery KW, Chasen M. Migration of central lines from the superior vena cava to the azygous vein. Clin Radiol. 2012;67(1):49–54.

37. Moureau N. Impact and Safety Associated with Accidental Dislodgement of Vascular Access Devices: A Survey of Professions, Settings, and Devices. JAVA - J Assoc Vasc Access [Internet]. 2018;23(4):203–15. Available from: https://doi.org/10.1016/j.java.2018.07.002

38. Chopra V, Anand S, Krein SL, Chenoweth C, Saint S. Bloodstream infection, venous thrombosis, and peripherally inserted central catheters: Reappraising the evidence. Am J Med [Internet]. 2012;125(8):733–41. Available from: http://dx.doi.org/10.1016/j.amjmed.2012.04.010

39. Fallouh N, McGuirk HM, Flanders SA, Chopra V. Peripherally inserted central catheter-associated deep vein thrombosis: A narrative review. Am J Med. 2015;128(7).

40. Unplanned hospital visits [Internet]. [cited 2019 Dec 23]. Available from: https://www.medicare.gov/hospitalcompare/Data/Hospital-returns.html

41. Koehler BE, Richter KM, Youngblood L, Cohen BA, Prengler ID, Cheng D, et al. Reduction of 30-day postdischarge hospital readmission or emergency department (ED) visit rates in high-risk elderly medical patients through delivery of a targeted care bundle. J Hosp Med. 2009;4(4):211–8.

42. Hohl CM, Partovi N, Ghement I, Wickham ME, McGrail K, Reddekopp LN, et al. Impact of early in-hospital medication review by clinical pharmacists on health services utilization. PLoS One. 2017;12(2):1–13.

43. Bedouch P, Charpiat B, Conort O, Rose FX, Escofier L, Juste M, et al. Assessment of clinical pharmacists' interventions in French Hospitals: Results of a multicenter study. Ann Pharmacother. 2008 Jul;42(7–8):1095–103.

44. Charpiat B, Bedouch P, Conort O, Rose FX, Juste M, Roubille R, et al. Opportunités d'erreurs médicamenteuses et interventions pharmaceutiques dans le cadre de la prescription informatisée : Revue des données publiées par les pharmaciens hospitaliers français. Vol. 70, Annales Pharmaceutiques Francaises. 2012. p. 62–74.

45. Charpiat B, Conort O, Juste M, Rose FX, Roubille R, Bedouch P, et al. Mise à disposition de l'outil de codification des interventions pharmaceutiques de la Société française de pharmacie clinique : bilan à 10 ans et perspectives. Vol. 50, Pharmacien Hospitalier et Clinicien. Elsevier Masson SAS; 2015. p. e15–24.

46. Mongaret C, Quillet P, Vo TH, Aubert L, Fourgeaud M, Michelet-Huot E, et al. Predictive factors for clinically significant pharmacist interventions at hospital admission. Vol. 97, Medicine (United States). Lippincott Williams and Wilkins; 2018.

47. Aguiar K da S, Santos JM Dos, Cambrussi MC, Picolotto S, Carneiro MB. Patient safety and the value of pharmaceutical intervention in a cancer hospital. Einstein (Sao Paulo). 2018;16(1):eAO4122.

48. Ha Vo T. Evaluation of the potential impact of pharmacist interventions : development and validation of the CLEO multidimensional tool [Internet]. [cited 2020 Feb 24]. Available from: https://tel.archives-ouvertes.fr/tel-01315619

49. Moons K, Waeyenbergh G, Pintelon L. Measuring the logistics performance of internal hospital supply chains – A literature study. Omega (United Kingdom) [Internet]. 2019;82:205–17. Available from: https://doi.org/10.1016/j.omega.2018.01.007

50. Chasseigne V, Leguelinel-Blache G, Nguyen TL, de Tayrac R, Prudhomme M, Kinowski JM, et al. Assessing the costs of disposable and reusable supplies wasted during surgeries. Int J Surg [Internet]. 2018;53:18–23. Available from: https://doi.org/10.1016/j.ijsu.2018.02.004

51. Société Française d'Hygiène Hospitalière (SF2H). Good practice and risk management for the use of PICC. 2013;(December).

52. Redmond P, Grimes TC, Mcdonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. Vol. 2018, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2018.

53. Andrade LF, Ludwig K, Goni JMR, Oppe M, de Pouvourville G. A French Value Set for the EQ-5D-5L. Pharmacoeconomics [Internet]. 2020;38(4):413–25. Available from:

https://doi.org/10.1007/s40273-019-00876-4

54. Chasseigne V, Bouvet S, Chkair S, Buisson M, Richard M, de Tayrac R, et al. Health economic evaluation of a clinical pharmacist's intervention on the appropriate use of devices and cost savings: A pilot study. Int J Surg. 2020;82(July):143–8.

55. Michel P, Lathelize M, Bru-Sonnet R, Perez C, Domecq S, Kret M, et al. Rapport final - Comparaison des deux études ENEIS 2004 et 2009. Drees, Ministère la santé. 2011;1–118.

56. Christensen LD, Holst M, Bech LF, Drustrup L, Nygaard L, Skallerup A, et al. Comparison of complications associated with peripherally inserted central catheters and Hickman™ catheters in patients with intestinal failure receiving home parenteral nutrition. Six-year follow up study. Clin Nutr [Internet]. 2016;35(4):912–7. Available from: http://dx.doi.org/10.1016/j.clnu.2015.06.009

57. Santacruz E, Mateo-Lobo R, Riveiro J, Nattero L, Vega-Piñero B, Lomba G, et al. Infectious complications in home parenteral nutrition: A long-term study with peripherally inserted central catheters, tunneled catheters, and ports. Nutrition. 2019;58:89–93.

58. Kilcup M, Schultz D, Carlson J, Wilson B. Postdischarge pharmacist medication reconciliation: Impact on readmission rates and financial savings. J Am Pharm Assoc. 2013;53(1):78–84.

59. Jones CD, Anthony A, Klein MD, Shakowski C, Smith HK, Go A, et al. The effect of a pharmacist-led multidisciplinary transitions-of-care pilot for patients at high risk of readmission. J Am Pharm Assoc. 2018 Sep 1;58(5):554–60.

60. Lussier ME, Evans HJ, Wright EA, Gionfriddo MR. The impact of community pharmacist involvement on transitions of care: A systematic review and meta-analysis. J Am Pharm Assoc [Internet]. 2019; Available from: https://doi.org/10.1016/j.japh.2019.07.002

61. Leguelinel-Blache G, Castelli C, Roux-Marson C, Bouvet S, Andrieu S, Cestac P, et al. Impact of collaborative pharmaceutical care on in-patients' medication safety: Study protocol for a stepped wedge cluster randomized trial (MEDREV study). Trials. 2018 Jan 8;19(1).

62. Ensing HT, Stuijt CCM, Van Den Bemt BJF, Van Dooren AA, Karapinar-Çarkit F, Koster ES, et al.

Identifying the optimal role for pharmacists in care transitions: A systematic review. Vol. 21, Journal of Managed Care Pharmacy. Academy of Managed Care Pharmacy (AMCP); 2015. p. 614–38.

63. Rigby K. Adverse events in health care: Setting priorities based on economic evaluation. J Qual Clin Pract. 1999;19(1):7–12.

64. Likert R. A technique for the measurement of attitudes. Arch Psychol. 1932;22(140):55.

65. Cook J V., Dickinson HO, Eccles MP. Response rates in postal surveys of healthcare professionals between 1996 and 2005: An observational study. BMC Health Serv Res. 2009;9:1–8.

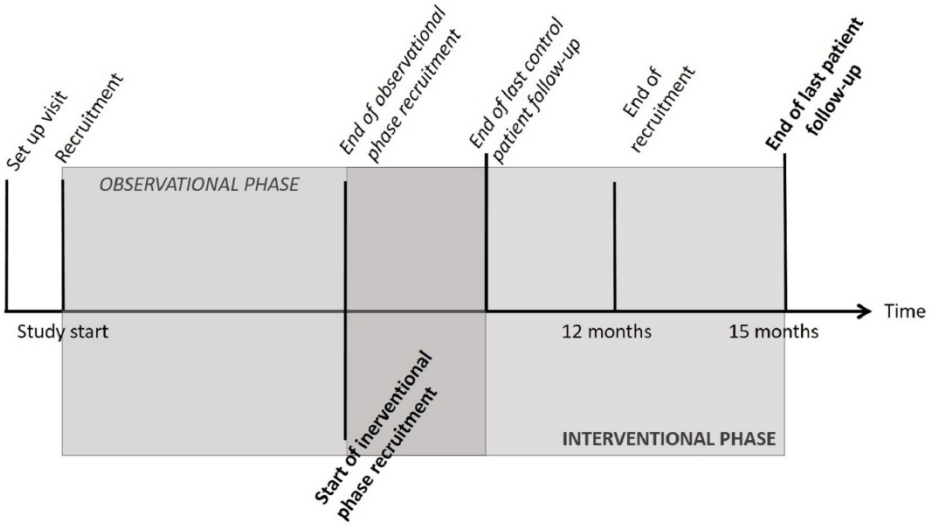

Figure 1: Study design.

159x91mm (300 x 300 DPI)

INFORMATION LEAFLET

INTEGRATION OF CLINICAL PHARMACY ALONG THE ENTIRE CARE PATHWAY OF PATIENTS IMPLANTED WITH A PICC-LINE

CLIPICC - RC31/18/0459

VERSION 2 DATED 03/02/2020

Study sponsor: Toulouse University Hospital Center

Acting Principal Investigator: Doctor Elodie CIVADE

Associate Principal Investigator: Doctor Charlotte LABORDE

Madam, Sir,

Your pharmacist has invited you to take part in a research study sponsored by the University Hospital Center of Toulouse. Before making a decision, it is important that you read these pages carefully as they will provide you with the necessary information about the different aspects of this research. Do not hesitate to ask your pharmacist or your doctor any questions you may have. Your participation is voluntary. If you do not wish to take part in this research, you will continue to receive the usual medical care in accordance with current knowledge.

❖ Why this research?

A PICC line is a central catheter or small tube designed to be inserted into a vein. It is placed at the edge of your arm and travels up into a vein that has larger flow. This allows for the administration of certain medications as well as repeated collection of blood samples if necessary. It is an implantable medical device.

Clinical pharmacy is a patient-centered healthcare discipline whose goal is to optimize therapeutic management at every stage of the care pathway. Clinical pharmacy procedures contribute to the safety, relevance and efficacy of drugs and medical devices. To achieve this, pharmacists must work in collaboration with other professionals such as the doctor, nurses, yourself and sometimes caregivers[1].

At present, clinical pharmacy in the field of medical devices (MD) is poorly developed in France. However, it has proven its effectiveness for medications. Thus, we would like to develop clinical pharmacy activities in the context of MDs, starting with the PICC line. We believe that we can improve the quality and safety of your hospital stay and home care through the clinical pharmacy activities detailed below.

❖ What is the purpose of this research?

Your usual treatments will not interfere with the study. You are hospitalized and require a PICC line for medication administration or repeated collection of blood samples. You will then go home with this device. The insertion of this medical device can sometimes lead to certain complications. We would like to show that the intervention of a clinical pharmacist during your treatment can prevent and therefore reduce the number of complications due to PICC lines by interacting with your doctor as needed and by giving you personalized advice on monitoring the PICC line. Similarly, your private nurse, your provider and/or your local pharmacist will receive information to help you follow up and monitor your PICC line.

❖ How is this research going to be carried out?

This is a single-center study at the UHC of Toulouse. Two successive phases are planned with 69 patients each: an observational phase and an interventional phase. Recruitment will last about 12 months to obtain the necessary number of patients.

[1] https://sfpc.eu/presentation/

Depending on when your PICC line is implanted, you may be in the observational phase without clinical pharmacy activities or in the interventional phase with clinical pharmacy activities. You cannot choose which phase you will be in.

- If you are in the **observational phase**:

Your treatment remains unchanged within the framework of standard medical care. We will only collect information without any intervention from the pharmacist. We will call you twice in the week following your discharge and then once a month for a maximum of 3 months.

- If you are in the **interventional phase**:

1. A **pharmaceutical analysis** of the PICC line prescription will be done. We are likely to discuss the prescription with the hospital doctor at this stage. Once the medical device is implanted, we will speak with your hospital nurse to ensure the best possible follow-up.

2. We will have carried **out logistical activities in the operating room where the PICC line is placed.** For example, we will have checked the quantities of devices needed for the installation and their expiry date, and we will also have checked that the lot number of the device is recorded in the hospital's database.

3. Once the PICC line has been implanted, you will return to your hospital ward for further treatment and then return home.

4. **We will analyze your discharge prescription** (medical devices and medicines) and may discuss it with the doctor.

5. You will have a **pharmaceutical discharge interview** of about 20 minutes in your hospital ward. This interview will allow us to discuss your medications and the PICC line with you (what the medications are used for, possible adverse effects, clinical laboratory monitoring if any, etc.). You will be able to ask any questions you may have (medical, clinical, etc.), and we will try to answer them as soon as possible. If further research needs to be done, we will call you to give you the answer. We will give you **information documents** on the PICC line to help you monitor it and be aware of the signs that you to the need to talk to a health professional as soon as possible. The goal is to prevent the most common complications. Finally, we will give you a sheet with the lot number of your PICC line so that you will have information about the implantation of this device in your possession. French law requires this.

6. A private nurse will redo your dressings at home. We will ask you to give us his or her name so we can contact him or her during the study. We will provide your nurse with your PICC line **information booklet** as well as **information on how to monitor and maintain** your PICC line.

7. We will ask you for the contact details of your pharmacist and your general practitioner so that we can contact them if necessary and in case of complications following insertion of the device. We will forward the **discharge prescription** to your pharmacist to ensure optimal **continuity of care**. We can also send him/her information about the PICC line.

8. Follow-up calls are scheduled throughout the study to **monitor and optimize your care**:

   8.1. You will be called personally by a pharmacist to follow-up on your treatment. We will ask you questions about the care of the dressing and about any complications. These calls will take place approximately on the 3rd and 7th day after the implantation and after 1 month, 2 months and 3 months. These calls will last approximately 15 minutes.
   8.2. Your nurse will also be called **to follow-up** on your care. We will ask him/her the same questions as you about the dressing and any complications. **Pharmaceutical advice** will be given if necessary to improve your care in collaboration with your private nurse. These calls will take place approximately on the 3rd and 7th day of the dressing care and after 1 month, 2 months and 3 months.
   8.3. Your local pharmacist will be contacted if necessary to note any changes in your treatment.

8.4. Your general practitioner will be contacted at the end of the 3-month follow-up period or earlier if necessary in the event of complications. Indeed, he/she is the one who knows your history best (in the event of a new medical condition or other diagnosis).

❖ **Who can participate?**

You can participate when all the following criteria are met:

- You are an adult, 18 years of age or older
- You are affiliated with the French social security system
- You live at home and can be reached by telephone
- You are scheduled to undergo insertion of a PICC line and you are destined to return home with this PICC line implanted
- Your profile suggests that your discharge prescription will include medications and a MD

You cannot be included if:

- You are a minor, under the age of 18
- You are not affiliated with the French social security system
- You do not live at home
    - You are institutionalized (specialized institutions)
    - You are living in a facility for dependent elderly persons
    - You live in a nursing home
    - You benefit from HAH (hospitalization at home)
- Your current health condition does not require a PICC line
- Your profile suggests that your discharge prescription will not include associated medications and MDs
- Your treatment plan does not include returning to home

Participation is voluntary. You will not be compensated for participating in this study.
No further examination is necessary before inclusion, only those corresponding to your treatment will be carried out.

❖ **What will you be asked to do?**

At the time of your inclusion, regardless of the phase:
We will ask you for your contact details and those of your GP and your pharmacist.

After the implantation of the PICC line, regardless of the phase:
We will ask you for the contact details of your private nurse who will monitor you at home.

Once you have returned home:
We will call you on the 3rd and 7th day after the implantation and 1 month, 2 months and 3 months after the implantation to:

- Gather information on the care of your dressing
- Collect information about possible complications due to the presence of the PICC line:
    - Related to your skin: any pain, redness or swelling
    - Related to the medical device: the catheter may become clogged, slightly cracked or displaced

We remind you that these events are relatively rare.

This phone call will last about 15 minutes.
If necessary, this information will be compared with the information given by your local healthcare professionals (doctors, nurse, healthcare provider and pharmacist) to confirm it.
If you are still hospitalized in the days following the insertion of the PICC line, we will visit you in your room on the 3rd and 7th day after the insertion.
You can withdraw from the study at any time.
If you withdraw from the study, you will continue to receive your current care.

❖ **What are the expected benefits?**

For you, the benefits are as follows:

- Due to additional information about your care and coordination between professionals, we believe you will benefit in the following ways:
  - Better care in the hospital and back home
  - Fewer complications due to the PICC line and associated medications
  - Your PICC line will be more comfortable, thanks to the care and maintenance tips
  - Improved quality of life, and better satisfaction with your care
- You will also have documents to refer to if you have any questions and you can always contact the hospital pharmacist and your local health care professionals if necessary
- We offer a close follow-up and a privileged relationship thanks to regular telephone calls

This research does not expose you to any additional risk in your care.

For science: clinical pharmacists offer a new way of working by accompanying you from when the medical device is implanted in the operating room to when you are at home by working more closely with hospital professionals and with healthcare professionals outside the hospital.

❖ **What are the possible constraints?**

You will be called five times after the insertion of your PICC line according to the research protocol, after you return home. Each phone call will last approximately 15 minutes. This call could disrupt your day, your work, and your activities. At any time, you can tell the person whose is calling you to call you back at a more convenient time.

❖ **What are the possible medical alternatives?**

If you do not participate in the research, you do not lose any chance of treatment.
You benefit from the usual care and standard practices in accordance with current knowledge.

❖ **What are the medical treatment modalities?**

If you are excluded from the research, you will be informed and you will continue to benefit from the usual medical care.

If the study is discontinued, the reason for the discontinuation will be noted. Your data will be used in the statistical analysis of the group you were in at the time of your study participation.
At the end of the study, the results will be communicated to you if you wish.

❖ **What are your rights?**

Your hospital pharmacist must provide you with all the necessary explanations about this research. If you wish to withdraw from the study at any time, no matter the reason, you will continue to benefit from medical follow-up and this will not affect your future care.

In the context of the research in which the Toulouse University Hospital offers you the opportunity to participate, your personal data will be processed electronically to enable the results of the research to be analyzed in the light of the research objective presented to you.
The party responsible for data processing is the UHC of Toulouse. The study investigator and other study staff will collect information about you, your health, your participation in the study, and, if applicable, your lifestyle. This information, called "Personal Information", is recorded on forms, called case report forms, provided by the sponsor. Only the information necessary for the processing and aim of the research will be collected. This data will be kept for the duration of the study until the final report or until the last publication and then archived in accordance with current regulations. To ensure the confidentiality of your personal information, neither your name nor any other information that would allow you to be identified directly will be entered in the case report form or in any other file that the study pharmacist will provide to the sponsor or the sponsor's authorized

representatives. Only a code and your initials will identify you. The code is used so that the study pharmacist can identify you if necessary.

In accordance with the provisions of the French Data Protection Act (Act No. 78-17 of January 6, 1978 on Data Processing, Data Files and Individual Liberties as amended by Act No. 2018-493 of June 20, 2018 on the Protection of Personal Data) and the General Data Protection Regulation (EU Regulation 2016/679), you have the right to access and rectify your personal information. In certain cases, you may also request that the processing of your personal information be restricted, object to certain types of processing of your personal information, and request that your personal information be deleted. However, certain data that was previously collected may not be erased if such deletion is likely to make it impossible or seriously compromise the achievement of the research objectives. You may exercise these rights by making a written request to the study investigator. The sponsor will respond to your request to the extent possible in accordance with its other legal and regulatory obligations and when required by law.

The sponsor may share personal information with regulatory agencies or research partners. These persons, companies and agencies may be in your country, in other EEA countries, or in other countries outside the EEA. Some non-EEA countries may not offer the same level of privacy protection as your country. The Sponsor will, however, maintain the confidentiality of all personal information it receives to the fullest extent possible within the limits of the law. The Sponsor will adopt appropriate contractual measures, including its certification under the Privacy Shield and its standard data protection clauses, to ensure that recipients outside the EEA provide an adequate level of protection for your personal information as set out in this form and in accordance with the law.

You also have the right to object to the transmission of data covered by professional secrecy that may be used during this research and processed. You can also access directly, or through the intermediary of the doctor of your choice, all your medical data pursuant to the provisions of Article L1111-7 of the French Public Health Code. These rights are exercised with the doctor or pharmacist who follows you in the context of the research and who knows your identity.

The competent authorities and the sponsor or its authorized representatives may also need access to your medical records and your study file to verify the data collected in the context of the study.

Your coded personal information may be used for further scientific research on your disease or other diseases in accordance with applicable laws and regulations.

If you have any additional questions about the collection or use of your personal information or the rights associated with this information, please contact the Data Protection Delegate of the UHC of Toulouse *(DPO@chu-toulouse.fr)* or the study investigator.

If you feel that your rights are not being respected, despite the measures put in place by the sponsor, you may file a complaint with the competent data protection supervisory authority in your country of residence (the CNIL for France).

In accordance with the French law No. 2012-300 of March 5, 2012 relating to research involving humans:

- This research has obtained a favorable opinion from the Committee for the Protection of Persons (CPP Sud Est 6).
- The sponsor of this research, the UHC of TOULOUSE has taken out civil liability insurance with Lloyd's Insurance Company S.A.
- This research falls within the framework of the Reference Methodology MR-001 of the CNIL (French National Commission for Information Technology and Civil Liberties)
- Persons who have suffered harm because of their participation in this study may assert their rights before the regional conciliation and compensation commission for medical accidents.
- When this research is completed, you will be kept personally informed of the results by the Investigator as soon as they are available, if you want.

After reading this information leaflet, do not hesitate to ask the investigator any questions you may have. After a waiting period, if you agree to participate in this research, you must complete and sign the Consent Form. A copy of the completed document will be given to you.

Thank you for your attention.

CONSENT FORM

INTEGRATION OF CLINICAL PHARMACY ALONG THE ENTIRE CARE PATHWAY OF PATIENTS IMPLANTED WITH A PICC-LINE

CLIPICC - RC31/18/0459

VERSION 2 OF 03/02/2020

Research sponsor: Toulouse University Hospital Center

Acting Principal Investigator: Doctor Elodie CIVADE

Associate Principal Investigator: Dr. Charlotte LABORDE

I, the undersigned..... (surname, first name) hereby certify that I have read and understood the information leaflet that was given to me.

I was able to ask any question I needed to ask to the investigator, Elodie CIVADE, who explained to me the nature, objectives, potential risks and constraints related to my participation in this study.

I am aware of the possibility that I may interrupt my participation in this study at any time without having to justify my decision and I will do my best to inform the pharmacist who is following me in the study. Of course, this will not affect the quality of subsequent care.

I have been assured that the decisions that are necessary for my health will be made at any time, in accordance with the current state of medical knowledge.

I have been informed that some of the information gathered during this study may be retained for future research purposes. I have also been informed of my right to object to such retention and subsequent use for research purposes.

I am aware that this study has received the favorable opinion of the Comité de Protection des Personnes Sud Est 6 and falls within the scope of MR001 of the Commission Nationale Informatique et Libertés (CNIL).

The sponsor of this study (CHU de Toulouse, 2 rue de Viguerie, 31000 Toulouse) has taken out a civil liability insurance policy in case of harm with Lloyd's Insurance Company S.A (BARCET 19001).

I accept that the persons collaborating in this study or authorized by the sponsor, as well as potential Health Authority representatives, have access to the information in the strictest confidentiality.

I accept that the data collected during this study may be subject to computerized processing under the responsibility of the sponsor.

I have noted that, in accordance with the provisions of the law on data processing, data files and freedoms and the general regulations on data protection, I have the right to access, rectify and delete data, to limit processing and to make the data portable. I also have a right to object to the transmission of data covered by professional secrecy which may be used in the context of this study and processed. These rights are exercised with the pharmacist who is following me in the context of this study and who knows my identity.

My consent in no way relieves the investigator and the research sponsor of their responsibilities towards me. I retain all legal rights.

The results of the study will be communicated to me directly, if I so wish, in accordance with the French law of 4 March 2002 on the rights of patients and the health care quality.

Having had sufficient time for thought before making my decision, I freely and voluntarily agree to participate in the CLIPICC study.

I may at any time request additional information from the pharmacist who has invited me to participate in this research, telephone number: 05 67 77 11 15 or 05 67 77 12 14

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Patient's signature:	Investigator's signature:

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 14
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	14
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	15

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	15
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3, 4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4,5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5,6,7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7,8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9,10

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, 7-8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4,5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care	4, 14

		providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	blinding is not possible in this study except for analysis
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14,15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10,11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10,11

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	before-after study: interim analysis not necessary
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5-8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A, no ancillary studies planned
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15,16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A , no ancillary trials.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16, all supplementary data through corresponding author

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	4, model as supplementary files
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A, no biological specimens

Notes:

- 11a: 8, 9, 10, 11, 12
- 17b: blinding is not possible in this study exept for analysis
- 21b: before-after study: interim analysis not necessary
- 26b: N/A, no ancillary studies planned
- 30: N/A , no ancillary trials.
- 31c: 24, all supplementary data through corresponding author
- 32: documents approuved by the ethic committee (24)
- 33: N/A, no biological specimens This checklist was completed on 07. April 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai