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TITLE PAGE

Title

The exit site assessment of central venous catheter among haemodialysis patients (EXITA study). Protocol for validation of a clinical scale in nine Spanish hospitals.

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ABSTRACT

Introduction

Haemodialysis patients with central venous catheter (CVC) are at increased risk of exit site infections (ESI) and catheter-related bloodstream infections, causing an increase of hospitalisation, morbidity, and mortality rates. The main aim of the present study is to develop and validate a haemodialysis catheter ESI assessment scale.

Methods and analysis

We propose to study and validate an instrument for the early detection of ESIs related to tunnelled haemodialysis CVCs (HD-CVCs). We will perform a scale validation study, by the Delphi method, with experts in the field of HD-CVCs, obtaining a qualitative analysis of the signs and symptoms derived from a systematic review. The principal outcome of the Delphi panel will be the initial version of the assessment scale. We will subject the scale items to the descriptive analysis and normality tests. We present a multicentre prospective cohort study with a sample of 470 HD-CVCs: 94 in the ESI group and 376 in the non-ESI group. To validate the proposed scale, the instrument score will be subjected to an exploratory descriptive analysis and to univariate and multivariate normality tests. Reliability will be checked by Cronbach's alpha coefficient. The results obtained will be compared with the gold standard (microbiological culture) using ROC curves.

Ethics and dissemination

Study has been approved from the Research Ethics Committee with Medical Products of Cantabria (approval code 2019.146). We will obtain informed consent from all participants before data collection. We will publish the study results in a peer-reviewed scientific journal.

Keywords: Exit site, Catheter-related infections, Haemodialysis, Validation study.

Strengths and limitations of this study

- In our knowledge, no validated scale exists for evaluating the exit site of central venous catheters (CVCs) for haemodialysis patients, despite the recommendations of clinical practice guidelines to perform a clinical evaluation at each haemodialysis session.
- The design of validated scale will improve the early detection of exit-site infection of central venous catheter, thus, daily use by healthcare professionals in haemodialysis units could provide a clinical and economic improvent and reduce morbidity and mortality among haemodialysis patients.
- The study will be carried out in nine hospitals of seven regions of the decentralised public health system in Spain, to maximise the external validity of the instrument to be developed. However, this multicentre approach will also influence clinical variability, in terms of CVC maintenance and the treatment approach adopted to local infections. A protocol on collecting samples for microbiological culture has been designed with the aim of avoiding bias.

Introduction

Haemodialysis patients need vascular access to facilitate renal replacement therapy, thus ensuring sufficient blood flow for dialysis, whilst maintaining clinical safety [1]. The method used to obtain this vascular access can have a significant impact on medium and long-term morbidity and mortality [2]. Numerous studies have shown that the use of a central venous catheter in haemodialysis (HD-CVC) is associated with higher morbidity and mortality than the use if an arteriovenous fistula [3–5]. However, approximately 50-80% of patients start haemodialysis therapy with a CVC in the USA and Europe [6–8], using this vascular access device among prevalent patients receiving haemodialysis in 30-40% of cases [1,6,7]. The advantage of CVCs is that they can be inserted immediately in emergencies (such as hyperkalaemia or acute lung oedema) and when the vascular bed is exhausted.

The incidence of central line-associated bloodstream infections (CLABSIs) following the insertion of a haemodialysis catheter is highly variable, ranging from 1.6 to 6.18 per 1000 catheter days for tunnelled catheters and from 1.4 to 8.3 per 1000 catheter days for non-tunnelled ones [9,10]. Similarly, the incidence of exit site infection ranges from 0.35 to 8.3 per 1000 catheter days for tunnelled catheters and from 8.2 to 16.75 per 1000 catheter days for non-tunnelled ones [9–12]. To some extent, this variability may be due to differences in the definitions of CLABSI and exit site infection, but it also reflects heterogeneous clinical management and poor adherence to clinical practice guidelines.

The estimated total cost of hospitalisation for a CVC-related infection ranges from $17,000 to $32,000 [13–15], according to the causative agent and the length of treatment/hospitalisation required. The use of a validated exit site assessment scale could reduce the appearance of local and systemic infectious complications by up to 10% [16], with the relevant savings in human, social and economic resources.

Clinical practice guidelines for the management of haemodialysis vascular access include recommendations related to the care of HD-CVCs during maintenance and insertion, aimed at minimising risk factors and avoiding potential complications, especially those related to infection (either local, at the exit site or in the subcutaneous tunnel, or CLABSI), which could lead the loss of vascular access or worse still to death [1,17–21]. The guidelines describe necessary precautions in the manipulation of the catheter (including care of the exit site and the surrounding skin) and the need for the patient to be instructed in self-care. The measures focused on exit site care include direct observation of this area during each haemodialysis session, to facilitate the early detection of infectious complications [1,17–21]. However, there is no universal definition of the signs and symptoms of exit site infection, and clinical practice guidelines on vascular access vary greatly in this regard [1,22–26]. In view of these considerations, we believe it necessary to seek a consensus regarding the definition of exit site infection, or at least its main signs and symptoms, to enable early identification.

Several studies bring evidence that central tunneled catheters exit site infection (ESI) may predispose to catheter-related bloodstream infection with occurrence in 4 to 20% cases of dialysis line-related sepsis [27,28]. Assessment scales for the exit site of other types of catheters, such as peripheral venous catheters [29–31] or peritoneal dialysis catheters [32–34], have been useful in clinical practice. A recent study shows a reduction of the ESI from 53,5% (CI 95% 35.9%-66.2%) to 18.6% (CI 95% 6.1-29,4%) ($p<0.001$) using a scale of this type in hemodialysis patients. Similarly, the study showed a reduction of CLABSIs from exerted positive impact on the frequency of the central tunneled catheters removal, which dropped from 39.5 to 20.9% ($p = 0.05$)[35]. However, this scale lacks a prior validation process. In our knowledge, no validated scale exists for evaluating exit site of HD-CVC. Therefore, we consider it necessary and timely to design and validate a scale for assessing the exit site of tunneled HD-CVC that underpins the recommendations of clinical practice guidelines.

Our primary objective is to validate a clinical scale for the exit site assessment of tunnelled HD-CVC to reduce infections in haemodialysis patients in Spanish hospitals. The secondary objectives are: 1) To evaluate the incidence of infectious complications in the exit site of HD-CVCs and their risk factors; and 2) To determine the relationship between the variability of the exit site care by healthcare professionals and the incidence of exit site infections.

Methods

Design

This study is intended to validate an instrument for the early detection of infection of the exit site of tunnelled HD-CVCs. The scale development will consist of two phases:

1.- Scale design. After identifying the clinical signs and symptoms, by a systematic review of the literature, they will be categorised by an international panel of experts in exit site care, using the Delphi technique. The Delphi protocol has been published recently [36]. The prioritisation thus obtained will be used to develop the preliminary version of the assessment scale we propose.

2.- Validation. We will conduct a prospective cohort study in a population of patients who have a HD-CVC, differentiating between those presenting exit site infection and those who are free of infection. Study period will be from 1 May 2021 to 30 June 2022. Study schedule of this phase is presented in figure 1.

Setting

This version of the assessment scale will then be subjected to a pilot and validation study with haemodialysis patients in seven regions (Autonomous Communities) of the decentralised Spanish health system at the following hospitals: NAMES OF HOSPITALS.

Subjects

The following inclusion criteria will be applied: patients with a tunnelled CVC one month after insertion (when the catheter is considered stable), undergoing renal replacement therapy with haemodialysis, aged at least 18 years, who consent to participate in the study. Patients who, due to their clinical and/or personal situation, cannot consent to participate will be excluded.

Sample size

The minimum sample size was calculated taking as a reference a mean ESI incidence of around 20% in Spain [37–39]. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral test, 94 cases in the ESI group and 376 in the non-ESI group to recognize as statistically significant relative risk greater than or equal to 1.9, assuming a rate of exposure of 0.2 in the non-ESI group. It has been anticipated a drop-out rate of 25%. In this consideration, the Poisson method was used. Simple size was calculated by Granmo Sample size and power calculator (Version 7.12 April 2012).

Data collection

The first version of the scale will be piloted in ten patients at each participating hospital, assessed by three nurses in each case. This initial approach is intended to obtain a linguistic validation of the instrument and thus assess its understandability and clarity. In addition, a qualitative analysis will be performed of the opinions expressed and according to the results obtained, the scale will be modified as appropriate, to produce the definitive assessment instrument.

This final version will then be taken as the exit site assessment method to be applied before each haemodialysis session at the participating hospitals (where the exit site treatment protocol will remain unchanged). A record will be kept of the data thus obtained, including clinical and catheter-related variables. If the patient presents more than one HD-CVC during the study

period, the corresponding data will be collected for each catheter. For every HD-CVC, an initial control culture will be obtained, based on a pericatheter skin smear from a healthy exit site (i.e., with no signs or symptoms of infection). During each haemodialysis session, the absence or presence of each item will be assessed. Nurses of the participating centers will receive training for the unequivocal identification of the signs/symptoms to be validated in order to eliminate observer bias. If any item is present, a microbiological study of pericatheter skin smears and/or exit site exudate will be carried out. A pericatheter skin swab culture will be repeated when the signs/symptoms disappear. For samples a dry cotton swab will be rubbed over a 2-cm^2 area around the insertion site, immediately after dressing removal, without performing skin disinfection [40,41]. Exclusion criteria to collect pericatheter skin smears: presence of local allergic reaction and /or bleeding. Data related to the microbiological study will be collected (Table 1).

HD-CVC exit site infection will be diagnose when the pericatheter skin smears and/or exit site exudate culture be positive (≥15CFU/ml by semiquantitative Maki's technique or ≥1,000 CFU/ml by Cleri´s technique) [40,41]. Skin contamination will not be considered infection and not be included in statistical analysis.

At each participating hospital, the local protocols applied regarding HD-CVC maintenance and the management/treatment of related infections, both local and systemic, will remain unchanged. The proposed assessment scale will continue to be applied until the necessary sample size is reached among the participating hospitals (within an estimated 8-12 months).

The presence of the sign/symptom will be scored with one point, while the absence will be scored with zero points.

Patient and Public Involvement

No patient involved.

Variables and definitions

Table 1 shows the variables to be considered and their definitions.

Table 1.- Variables and definitions

Group	Variable	Definition
Clinical variables	Age (continuous quantitative)	
	Sex (qualitative)	
	Kidney disease aetiology (qualitative)	According to the ERA/EDTA coding
	Degree of comorbidity (qualitative)	According to the Modified Charlson Index for patients with kidney failure
	Months in kidney replacement therapy with hemodialysis (quantitative)	Months (n)
Catheter-related variables	Type (qualitative)	Tunnelled or non-tunnelled
	Catheter design (qualitative)	One exit orifice Two exit orifices
	Duration of catheter insertion (quantitative)	Days elapsed since the insertion
	Venous insertion (qualitative)	Subclavian (left or right) Jugular (left or right) Other
	Previous CVC-related infections (qualitative)	ES infection: Yes / No Tunnel infection: Yes / No Bacteraemia: Yes / No
Variables related to local CVC maintenance	Frequency of ES attention (qualitative)	At each dialysis session - Weekly - As required – Other frequency
	Antiseptic (qualitative)	Chlorhexidine aqueous solution 0.5% Chlorhexidine alcohol solution 2% Povidone iodine Alcohol 70% Other antiseptic Antibiotic instillation
	Dressing (qualitative)	Gauze Partially reinforced transparent polyurethane Clear, fully reinforced polyurethane Transparent polyurethane with chlorhexidine gluconate window Other
	Frequency of ES evaluation (qualitative)	At each dialysis session Weekly As necessary Other
Variables concerning catheter-related infections during follow-up	Presence of scale items (qualitative/ quantitative)	Yes= 1 point / No= 0 points
	Culture (qualitative)	Type of sample collected (pericatheter smear and/or exudate), culture method, result (including microorganisms if positive culture).

Data analysis

Total score will be calculated adding the points in the presence or absence of the signs and symptoms to be validated. To validate the proposed scale, the instrument score will be subjected to an exploratory descriptive analysis (central tendency, dispersion, asymmetry and kurtosis) and to univariate and multivariate normality tests. The reliability of the scale will be checked by determining the Cronbach's alpha coefficient for each item on the scale. For the decision validity analysis, the results obtained will be compared with the gold standard (microbiological culture of either the skin surrounding the exit site, or of the exit site exudate) using ROC curves of sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratio (for total score and range of scores). In addition, the Youden index will be calculated to optimise the cut-off point of the scale (Youden = sensitivity + specificity-1). These analyses will be carried out for each item of the scale separately, and also for various combinations of items.

To address the secondary aims of this study, a descriptive analysis of the variables will be performed, including the distribution of the phenomena under study within each of the dialysis units concerned. A multiple regression analysis will be carried out to determine the association between the presence of infectious complications (as determined by microbiological tests) and the clinical variables, catheter-related variables and local catheter maintenance policies. Statistical analysis will be performed using SPSS software (version 20.0) and MedCalc software (version 19.6).

Ethics and dissemination

The study will not involve any clinical intervention or change in usual practice. The patients concerned will be asked by the clinician nurse to provide signed informed consent and will be

given clear written information about the purposes and implications of the research. The computerised database will not contain patient identification data. The individuals involved in compiling the data will sign a confidentiality agreement. The Research Ethics Committee with Medical Products of Cantabria (CEIm of Cantabria, approval code 2019.146) has approved this protocol study. We will send the findings of this study to a peer-reviewed scientific journal for publication.

Discussion

Using a validated instrument to assess the exit site of the HD-CVC will make observations more objective, facilitate a uniform classification and thus enable results to be readily compared. The use of a validated exit site assessment scale can reduce the likelihood of local and systemic infectious complications in hemodialisys patients; reducing morbidity, hospitalizations, mortality and associated costs. Moreover, its use will provide continuity of care and a documented record of exit site evolution. This instrument will also help researchers achieve a uniform measure of the effects of interventions on the incidence of infectious exit site complications. Finally, this instrument will enable patients to receive objective information about the status of the catheter exit site, accustoming them to identify signs of infection at an early stage and fostering self-care.

Mapping clinical variability in issues related to maintaining the exit site, as proposed in this study, will provide valuable support for future research into the implementation of evidence-based measures.

As limitation, each patient included may present one or multiple episodes of HD-CVC exit site infection without being able to formally verify that the different episodes from a single patient are independent of each other. The study will be carried out in nine hospitals of seven regions

of the decentralised public health system in Spain, to maximise the external validity of the instrument to be developed. However, this multicentre approach will also influence clinical variability, in terms of CVC maintenance and the treatment approach adopted to local infections. A protocol on collecting samples for microbiological culture has been designed with the aim of avoiding bias.

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Figure Legend

Figure 1.- Validation study schedule.

Authors' contributions: JLCS coordinates the research team and is responsible for reporting to Ethics Committees and every institution involved in the study. JLCS and IBM revised previous literature on haemodialysis CVC guidelines and recommendations and previous ES assessment scales. JLCS, IBM and JEPG designed the scale design and data collection methods, together with NMS, RPA and IFF. JLCS, IBM and JEPG audited the study design, especially concerning the proposed statistical analysis. JLCS, IBM and JEPG wrote the first version of the protocol, which was later edited by all the authors.

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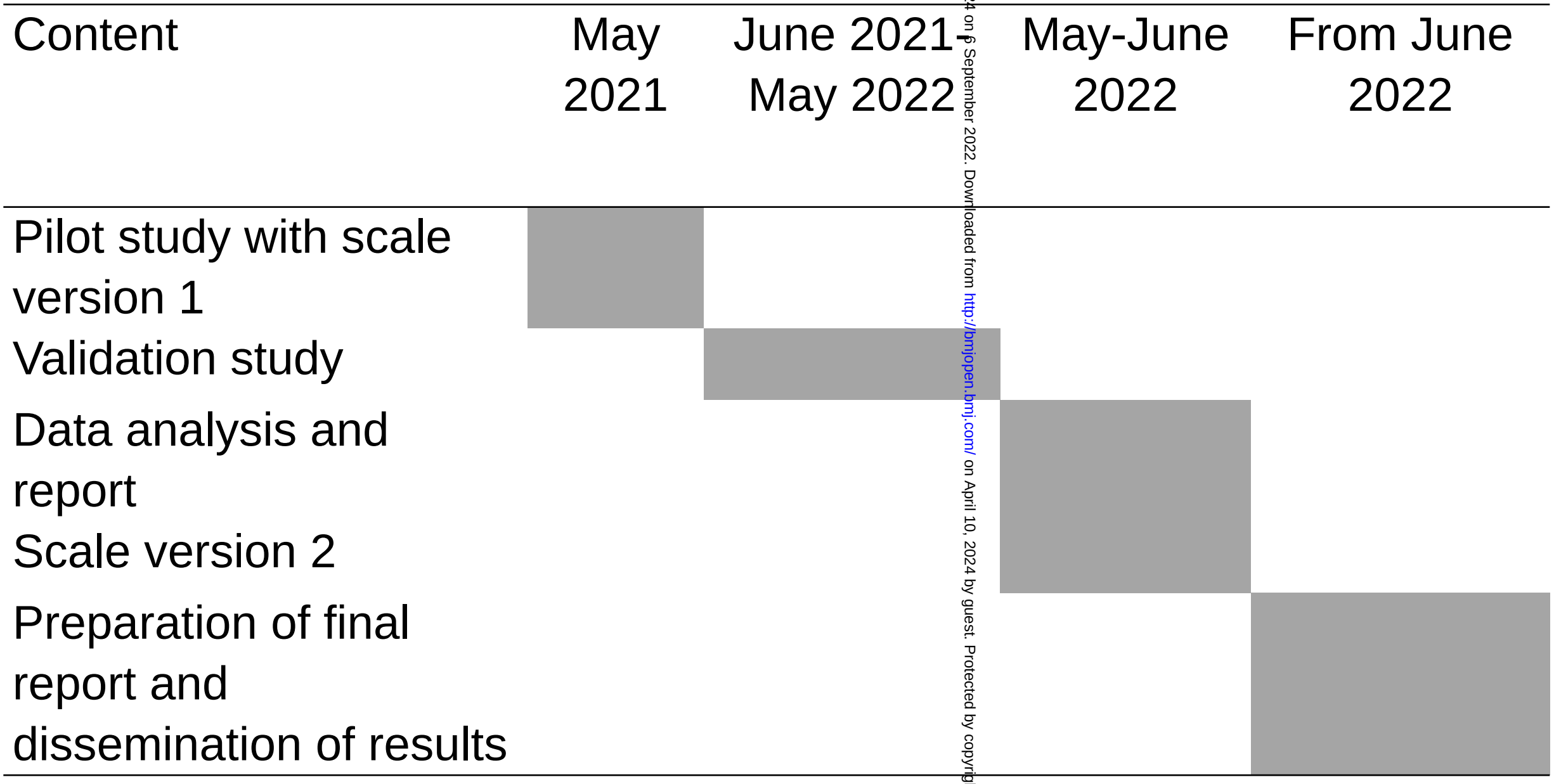

Figure 1.- Validation study schedule.

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Validity of a catheter exit site clinical assessment scale for the early detection of exit site infections in patients on haemodialysis with a central venous catheter: protocol for a multicentre validation study in Spain (EXITA study)

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Title

Validity of a catheter exit site clinical assessment scale for the early detection of exit site infections in patients on haemodialysis with a central venous catheter: protocol for a multicentre validation study in Spain (EXITA study)

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ABSTRACT

Introduction

Haemodialysis patients with central venous catheter (HD-CVC) are at increased risk of exit site infections (ESI) and catheter-related bloodstream infections, causing an increase of hospitalisation, morbidity, and mortality rates. The main aim of the EXITA study is to develop and validate an instrument for the early detection of HD-CVC ESIs.

Methods and analysis

EXITA study proposes a multicentre prospective cohort study to validate the proposed instrument with a sample of 457 HD-CVCs: 92 in the ESI group and 365 in the non-ESI group. Sample size was calculated using Epidat 4.2™ software, with 95% and 90% expected sensitivity and specificity respectively, an ESI incidence around 20% and 5% to 10% precision range. During each haemodialysis session, the absence or presence of each item will be assessed by nurses. If any item is present, a microbiological study of pericatheter skin smears and/or exit site exudate will be carried out. HD-CVC ESI will be diagnosed when the pericatheter skin smears and/or exit site exudate culture be positive (≥15 CFU/ml by semiquantitative Maki's technique or ≥1,000 CFU/ml by Cleri´s technique). The presence of the sign/symptom will be scored with one point, while the absence will be scored with zero points. The validity of the total score of scale will be analysed using specificity, sensitivity, positive and negative likelihood ratios (LH+, LH-), receiver operating characteristic (ROC) curves, area under the ROC curve (AUC), and relative (95% CI).

Ethics and dissemination

Study has been approved from the Research Ethics Committee with Medical Products of Cantabria (approval code 2019.146). We will obtain informed consent from all participants before data collection. We will publish the study results in a peer-reviewed scientific journal.

Keywords: Exit site, Catheter-related infections, Haemodialysis, Validation study.

Strengths and limitations of this study

- This is the first study based on a consistent statistical approach to evaluate the validity of a catheter exit site clinical assessment scale in patients on haemodialysis for the early detection of exit site infections.
- The ítems of scale are based in a previous systematic review and a consensus of an international panel of experts in care of vascular access in patients on haemodialysis, that provides robustness in content validity.
- The study will be carried out in nine hospitals to maximise the external validity of the scale.
- As limitation, each patient included may present one or multiple episodes of exit site infections without being able to formally verify that the different episodes from a single patient are independent of each other.

Introduction

Patients on haemodialysis need vascular access to facilitate renal replacement therapy, thus ensuring sufficient blood flow for dialysis, whilst maintaining clinical safety [1]. The method used to obtain this vascular access can have a significant impact on medium and long-term morbidity and mortality [2]. Numerous studies have shown that the use of a central venous catheter in haemodialysis (HD-CVC) is associated with higher morbidity and mortality than the use if an arteriovenous fistula [3–5]. However, approximately 50-80% of patients start haemodialysis therapy with a CVC in the USA and Europe [6–8], using this vascular access device among prevalent patients receiving haemodialysis in 30-40% of cases [6,7,9]. The advantage of CVCs is that they can be inserted immediately in emergencies (such as hyperkalaemia or acute lung oedema) and when the vascular bed is exhausted.

The incidence of central line-associated bloodstream infections (CLABSIs) following the insertion of a haemodialysis catheter is highly variable, ranging from 1.6 to 6.18 per 1000 catheter days for tunnelled catheters and from 1.4 to 8.3 per 1000 catheter days for non-tunnelled ones [10,11]. Similarly, the incidence of exit site infection (ESI) ranges from 0.35 to 8.3 per 1000 catheter days for tunnelled catheters and from 8.2 to 16.75 per 1000 catheter days for non-tunnelled ones [10–13]. To some extent, this variability may be due to differences in the definitions of CLABSI and ESI, but it also reflects heterogeneous clinical management and poor adherence to clinical practice guidelines.

The estimated total cost of hospitalisation for a CVC-related infection ranges from $17,000 to $32,000 [14–16], according to the causative agent and the length of treatment/hospitalisation required. The use of a validated exit site assessment scale could reduce the appearance of local and systemic infectious complications by up to 10% [17], with the relevant savings in human, social and economic resources.

Clinical practice guidelines for the management of haemodialysis vascular access include recommendations related to the care of HD-CVCs during maintenance and insertion, aimed at minimising risk factors and avoiding potential complications, especially those related to infection (either local, at the exit site or in the subcutaneous tunnel, or CLABSI), which could lead the loss of vascular access or worse still to death [9,18–22]. The guidelines describe necessary precautions in the manipulation of the catheter (including care of the exit site and the surrounding skin) and the need for the patient to be instructed in self-care. The measures focused on exit site care include direct observation of this area during each haemodialysis session, to facilitate the early detection of infectious complications [9,18–22]. However, there is no universal definition of the signs and symptoms of ESI, and clinical practice guidelines on vascular access vary greatly in this regard [9,23–27]. In view of these considerations, we believe it necessary to seek a consensus regarding the definition of ESI, or at least its main signs and symptoms, to enable early identification.

Several studies bring evidence that central tunneled catheters ESI may predispose to CLABSI with occurrence in 4 to 20% cases of dialysis line-related sepsis [27,28]. Assessment scales for the exit site of other types of catheters, such as peripheral venous catheters [30–32] or peritoneal dialysis catheters [33–35], have been useful in clinical practice. A recent study shows a reduction of the ESI from 53,5% (CI 95% 35.9%-66.2%) to 18.6% (CI 95% 6.1-29,4%) ($p<0.001$) using a scale of this type in patients on haemodialysis. Similarly, the study showed a reduction of CLABSIs from exerted positive impact on the frequency of the central tunneled catheters removal, which dropped from 39.5 to 20.9% ($p = 0.05$)[36]. However, this scale lacks a prior validation process. In our knowledge, no validated scale exists for evaluating exit site of HD-CVC.

Current clinical practice guidelines on vascular access for haemodialysis and infection control do not provide a universal definition regarding exit site infection [1,23–26]. In this respect, the

2019 update of the KDOQI Clinical Practice Guideline [23] indicates as a recommended area for future research "further validation studies of diagnostic criteria for exit site and tunnel infections in haemodialysis patients".

Therefore, we consider it necessary and timely to design and validate a scale for assessing the exit site of tunneled HD-CVC that underpins the recommendations of clinical practice guidelines.

EXIT site Assessment (EXITA) study primary objective is to validate a clinical scale for the exit site assessment of tunnelled HD-CVC to reduce infections in patients on haemodialysis in Spanish hospitals. The secondary objectives are: 1) To evaluate the incidence of infectious complications in the exit site of HD-CVCs and their risk factors; and 2) To determine the relationship between the variability of the exit site care by healthcare professionals and the incidence of ESI.

Methods and analysis

Design

EXITA study is intended to validate an instrument for the early detection of ESI in tunnelled HD-CVCs. The scale development will consist of two phases:

1.- Scale design. After identifying the clinical signs and symptoms, by a scoping review of the literature, they will be categorised by an international panel of experts in HD-CVC exit site care, using the Delphi technique. The Delphi protocol has been published recently [37]. The prioritisation thus obtained will be used to develop the preliminary version of the assessment scale we propose.

2.- Validation. We will conduct a prospective cohort study in a population of patients who have a HD-CVC, differentiating between those presenting ESI and those who are free of infection.

Timeline for the study

Pilot study with scale version 1 will take place in May 2021. Patients' recruitment take place during validation study period: this period will be from 1 May 2021 to 30 June 2022. Data analysis, the review of the behavior of the items of the scale and its version 2, are scheduled to take place in May-June 2022, after reaching the planned sample size. Data analysis and report Timeline of EXITA study is presented in figure 1.

Setting

This version of the assessment scale will then be subjected to a pilot and validation study with patients on haemodialysis in seven regions (Autonomous Communities) of the decentralised Spanish health system at the following hospitals: NAMES OF HOSPITALS.

Subjects

The following inclusion criteria will be applied: patients with a tunnelled CVC one month after insertion (when the catheter is considered stable), undergoing renal replacement therapy with haemodialysis, aged at least 18 years, who consent to participate in the study. Patients who, due to their clinical and/or personal situation, cannot consent to participate will be excluded.

Sample size

The minimum sample size was calculated taking as a reference a mean ESI incidence around 20% in Spain [38–40], with an expected sensitivity of 95% and an expected specificity of 90%. We calculate that 92 patients should be included in the ESI group in order to estimate the presence of exit site infection, with 95% confidence level and a precision of ±10 percentage units. Similarly, 365 patients should be included in the non-ESI group in order to estimate, with 95% confidence level and a precision of ±5 percentage units. Sample size was calculated using Epidat 4.2™ software [41].

Data collection

The first version of the scale will be piloted in ten patients at each participating hospital, assessed by three nurses in each case. This initial approach is intended to obtain a linguistic validation of the instrument and thus assess its understandability and clarity. In addition, a qualitative analysis will be performed of the opinions expressed and according to the results obtained, the scale will be modified as appropriate, to produce the definitive assessment instrument.

This final version will then be taken as the exit site assessment method to be applied before each haemodialysis session at the participating hospitals (where the exit site treatment protocol will remain unchanged). A record will be kept of the data thus obtained, including clinical and catheter-related variables. If the patient presents more than one HD-CVC during the study period, the corresponding data will be collected for each catheter. For every HD-CVC, an initial control culture will be obtained, based on a pericatheter skin smear from a healthy exit site (i.e., with no signs or symptoms of infection). During each haemodialysis session, the absence or presence of each item will be assessed. Nurses of the participating centers will receive training for the unequivocal identification of the signs/symptoms to be validated in order to eliminate observer bias. If any item is present, a microbiological study of pericatheter skin smears and/or exit site exudate will be carried out. A pericatheter skin swab culture will be repeated when the signs/symptoms disappear. For samples a dry cotton swab will be rubbed over a 2-cm^2 area around the insertion site, immediately after dressing removal, without performing skin disinfection [1,42]. Exclusion criteria to collect pericatheter skin smears: presence of local allergic reaction and /or bleeding. Data related to the microbiological study will be collected (Table 1).

HD-CVC ESI will be diagnose when the pericatheter skin smears and/or exit site exudate culture be positive (≥15 CFU/ml by semiquantitative Maki's technique or ≥1,000 CFU/ml by Cleri´s technique) [1,42]. Skin contamination will not be considered infection and not be included in statistical analysis.

At each participating hospital, the local protocols applied regarding HD-CVC maintenance and the management/treatment of related infections, both local and systemic, will remain unchanged. The proposed assessment scale will continue to be applied until the necessary sample size is reached among the participating hospitals (within an estimated 8-12 months).

The presence of the sign/symptom will be scored with one point, while the absence will be scored with zero points.

Patient and Public Involvement

No patient involved.

Variables and definitions

Table 1 shows the variables to be considered and their definitions.

Table 1.- Variables and definitions

Group	Variable	Definition
Clinical variables	Age (continuous quantitative)	Years (n)
	Sex (qualitative)	Male Female
	Kidney disease aetiology (qualitative)	According to the ERA/EDTA coding
	Degree of comorbidity (qualitative)	According to the Modified Charlson Index for patients with kidney failure
	Months in kidney replacement therapy with hemodialysis (quantitative)	Months (n)
Catheter-related variables	Catheter design (qualitative)	One exit site Two exit sites
	Duration of catheter insertion (quantitative)	Days elapsed since the insertion
	Venous insertion (qualitative)	Subclavian (left or right) Jugular (left or right) Other
	Previous CVC-related infections (qualitative)	Exit site infection: Yes / No Tunnel infection: Yes / No Bacteraemia: Yes / No
Variables related to local CVC maintenance	Frequency of dressing change (qualitative)	At each dialysis session Weekly As required Other frequency
	Antiseptic (qualitative)	Chlorhexidine aqueous solution 0.5% Chlorhexidine alcohol solution 2% Povidone iodine Alcohol 70% Other antiseptic Antibiotic instillation
	Dressing (qualitative)	Gauze Partially reinforced transparent polyurethane Fully reinforced transparent polyurethane Transparent polyurethane with chlorhexidine gluconate window Other
	Frequency of ES evaluation (qualitative)	At each dialysis session Weekly As necessary Other
Variables concerning catheter-related infections during follow-up	Presence of scale items (qualitative/ quantitative)	Yes= 1 point No= 0 points

	Culture (qualitative)	Type of sample collected (pericatheter smear and/or exudate), culture method, result (including microorganisms if positive culture).

Data analysis

Total scale score will be calculated adding the points in the presence or absence of the signs and symptoms to be validated. The total score will be subjected to an exploratory descriptive analysis (central tendency, dispersion, asymmetry and kurtosis) and to univariate and multivariate normality tests. For the decision validity analysis, the total score obtained will be compared with the gold standard (microbiological culture of either the skin surrounding the exit site, or of the exit site exudate). The validity of the scale will be analysed using specificity, sensitivity, positive and negative likelihood ratios (LH+, LH-), receiver operating characteristic (ROC) curves, area under the ROC curve (AUC), and relative (95% CI)[43]. An AUC value >0.5 and close to 1 will indicate a good level of predictability of the scale. In addition, the Youden index will be calculated to optimise the cut-off point of the scale (Youden = sensitivity + specificity-1). These analyses will be carried out for each item of the scale separately, and also for various combinations of items.

To address the secondary aims of this study, a descriptive analysis of the variables will be performed, including the distribution of the phenomena under study within each of the dialysis units concerned. A multiple regression analysis will be carried out to determine the association between the presence of infectious complications (as determined by microbiological tests) and the clinical variables, catheter-related variables and local catheter maintenance policies. Statistical analysis will be performed using SPSS software (version 20.0) and MedCalc software (version 19.6).

Ethics and dissemination

The study will not involve any clinical intervention or change in usual practice. The patients concerned will be asked by the clinician nurse to provide signed informed consent and will be given clear written information about the purposes and implications of the research. The computerised database will not contain patient identification data. The individuals involved in compiling the data will sign a confidentiality agreement. The Research Ethics Committee with Medical Products of Cantabria (CEIm of Cantabria, approval code 2019.146) has approved this protocol study. We will send the findings of this study to a peer-reviewed scientific journal for publication.

Discussion

Using a validated instrument to assess the exit site of the HD-CVC will make observations more objective, facilitate a uniform classification and thus enable results to be readily compared. The use of a validated exit site assessment scale can reduce the likelihood of local and systemic infectious complications in patients on haemodialysis; reducing morbidity, hospitalizations, mortality and associated costs. Moreover, its use will provide continuity of care and a documented record of exit site evolution. This instrument will also help researchers achieve a uniform measure of the effects of interventions on the incidence of ESI complications. Finally, this instrument will enable patients to receive objective information about the status of the catheter exit site, accustoming them to identify signs of infection at an early stage and fostering self-care.

Mapping clinical variability in issues related to maintaining the exit site, as proposed in this study, will provide valuable support for future research into the implementation of evidence-based measures.

Strengths and limitations

As limitation, each patient included may present one or multiple episodes of HD-CVC ESI without being able to formally verify that the different episodes from a single patient are independent of each other. The study will be carried out in nine hospitals of seven regions of the decentralised public health system in Spain, to maximise the external validity of the scale to be developed. However, this multicentre approach will also influence clinical variability, in terms of CVC maintenance and the treatment approach adopted to local infections. A protocol on collecting samples for microbiological culture has been designed with the aim of avoiding bias.

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Figure Legend

Figure 1.- Timeline of EXITA study.

Contributors: JLCS coordinates the research team and is responsible for reporting to Ethics Committees and every institution involved in the study. JLCS and IBM revised previous literature on haemodialysis CVC guidelines and recommendations and previous ES assessment scales. JLCS, IBM and JEPG designed the scale design and data collection methods, together with NMS, RPA and IFF. JLCS, IBM and JEPG audited the study design, especially concerning the proposed statistical analysis. JLCS, IBM and JEPG wrote the first version of the protocol, which was later edited by all the authors.

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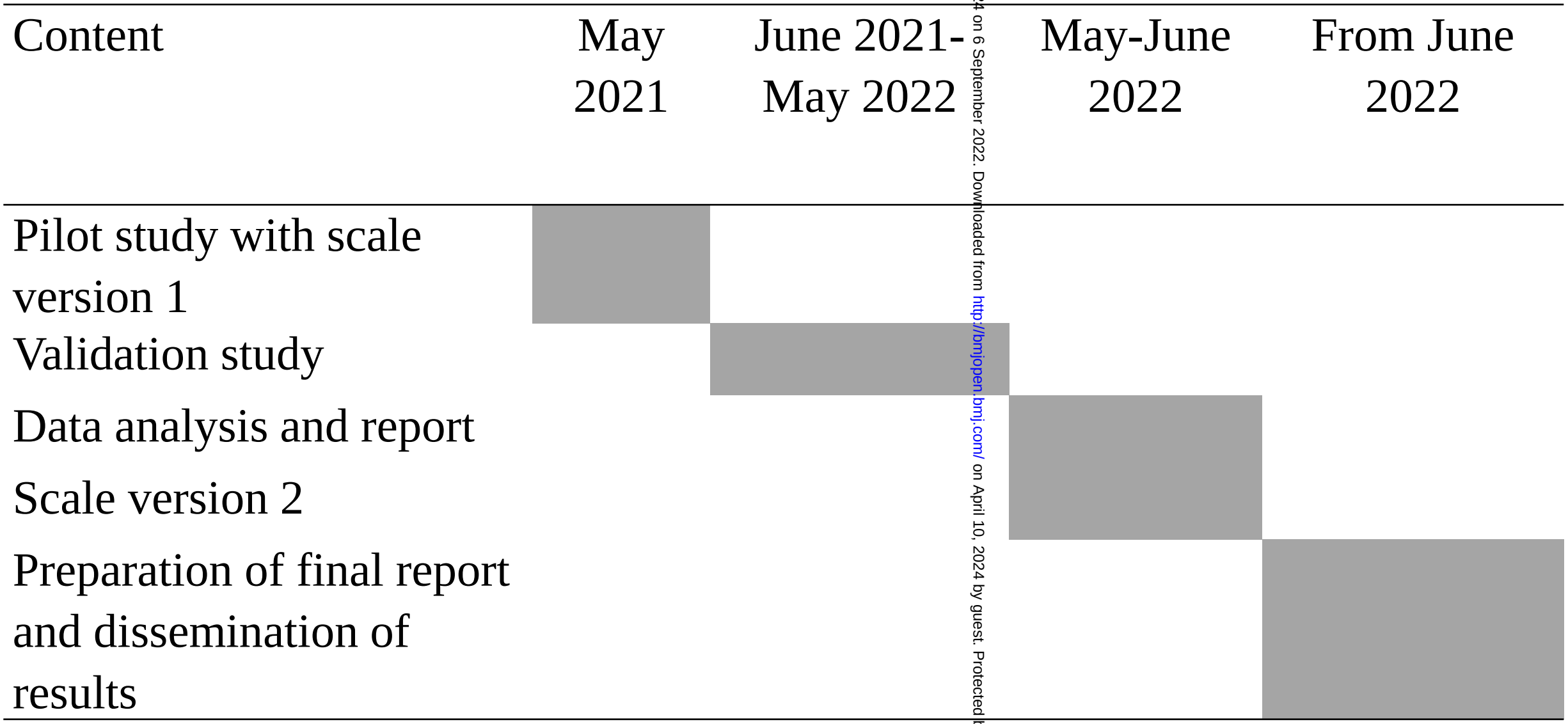

Figure 1.- Timeline of EXITA study.

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Validity of a catheter exit site clinical assessment scale for the early detection of exit site infections in patients on haemodialysis with a central venous catheter: protocol for a multicentre validation study in Spain (EXITA study)

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ABSTRACT

Introduction

Haemodialysis patients with central venous catheter (HD-CVC) are at increased risk of exit site infections (ESI) and catheter-related bloodstream infections, causing an increase of hospitalisation, morbidity, and mortality rates. The main aim of the EXITA study is to develop and validate an instrument for the early detection of HD-CVC ESIs.

Methods and analysis

EXITA is a multicentre prospective cohort study to validate the proposed instrument with a sample of 457 HD-CVCs: 92 in the ESI group and 365 in the non-ESI group. Sample size was calculated using Epidat 4.2™ software, with 95% and 90% expected sensitivity and specificity respectively, an ESI incidence around 20% and 5% to 10% precision range. During each haemodialysis session, the absence or presence of each item will be assessed by nurses. If any item is present, a microbiological study of pericatheter skin smears and/or exit site exudate will be carried out. HD-CVC ESI will be diagnosed when the pericatheter skin smears and/or exit site exudate culture be positive (≥15 CFU/ml by semiquantitative Maki's technique or ≥1,000 CFU/ml by Cleri´s technique). To validate the scale, a logistic regression analysis will be performed: the β coefficients of each of the signs/symptoms of the scale to be validated will be estimated. We will use logit function and calculate ESI probability = $e^{\text{logit ESI}}/1+ e^{\text{logit ESI}}$.

Ethics and dissemination

Study has been approved by the Research Ethics Committee with Medical Products of Cantabria (approval code 2019.146). We will obtain informed consent from all participants before data collection. We will publish the study results in a peer-reviewed scientific journal.

Keywords: Exit site, Catheter-related infections, Haemodialysis, Validation study.

Strengths and limitations of this study

- To our knowledge, this is the first study based on a consistent statistical approach to evaluate the validity of a catheter exit site clinical assessment scale in patients on haemodialysis for the early detection of exit site infections.
- The ítems of scale are based in a previous systematic review and a consensus of an international panel of experts in care of vascular access in patients on haemodialysis, that provides robustness in content validity.
- The study will be carried out in nine hospitals to maximise the external validity of the scale.
- One limitation of the study is that each patient included may present one or multiple episodes of exit site infections without being able to formally verify that the different episodes from a single patient are independent of each other.

Introduction

Patients on haemodialysis need vascular access to facilitate renal replacement therapy, thus ensuring sufficient blood flow for dialysis, whilst maintaining clinical safety [1]. The method used to obtain this vascular access can have a significant impact on medium and long-term morbidity and mortality [2]. Numerous studies have shown that the use of a central venous catheter in haemodialysis (HD-CVC) is associated with higher morbidity and mortality than the use if an arteriovenous fistula [3–5]. However, approximately 50-80% of patients start haemodialysis therapy with a CVC in the USA and Europe [6–8], using this vascular access device among prevalent patients receiving haemodialysis in 30-40% of cases [1,6,7]. The advantage of CVCs is that they can be inserted immediately in emergencies (such as hyperkalaemia or acute lung oedema) and when the vascular bed is exhausted.

The incidence of central line-associated bloodstream infections (CLABSIs) following the insertion of a haemodialysis catheter is highly variable, ranging from 1.6 to 6.18 per 1000 catheter days for tunnelled catheters and from 1.4 to 8.3 per 1000 catheter days for non-tunnelled ones [9,10]. Similarly, the incidence of exit site infection (ESI) ranges from 0.35 to 8.3 per 1000 catheter days for tunnelled catheters and from 8.2 to 16.75 per 1000 catheter days for non-tunnelled ones [9–12]. To some extent, this variability may be due to differences in the definitions of CLABSI and ESI, but it also reflects heterogeneous clinical management and poor adherence to clinical practice guidelines.

The estimated total cost of hospitalisation for a CVC-related infection ranges from $17,000 to $32,000 [13–15], according to the causative agent and the length of treatment/hospitalisation required. The use of a validated exit site assessment scale could reduce the appearance of local and systemic infectious complications by up to 10% [16], with the relevant savings in human, social and economic resources.

Clinical practice guidelines for the management of haemodialysis vascular access include recommendations related to the care of HD-CVCs during maintenance and insertion, aimed at minimising risk factors and avoiding potential complications, especially those related to infection (either local, at the exit site or in the subcutaneous tunnel, or CLABSI), which could lead the loss of vascular access or worse still to death [1,17–21]. The guidelines describe necessary precautions in the manipulation of the catheter (including care of the exit site and the surrounding skin) and the need for the patient to be instructed in self-care. The measures focused on exit site care include direct observation of this area during each haemodialysis session, to facilitate the early detection of infectious complications [1,17–21]. However, there is no universal definition of the signs and symptoms of ESI, and clinical practice guidelines on vascular access vary greatly in this regard [1,18,22–25]. In view of these considerations, we believe it necessary to seek a consensus regarding the definition of ESI, or at least its main signs and symptoms, to enable early identification.

Several studies bring evidence that central tunneled catheters ESI may predispose to CLABSI with occurrence in 4 to 20% cases of dialysis line-related sepsis [26,27]. Assessment scales for the exit site of other types of catheters, such as peripheral venous catheters [28–30] or peritoneal dialysis catheters [31–33], have been useful in clinical practice. A recent study shows a reduction of the ESI from 53,5% (CI 95% 35.9%-66.2%) to 18.6% (CI 95% 6.1-29,4%) ($p<0.001$) using a scale of this type in patients on haemodialysis. Similarly, the study showed a reduction of CLABSIs from exerted positive impact on the frequency of the central tunneled catheters removal, which dropped from 39.5 to 20.9% ($p = 0.05$) [34]. However, this scale lacks a prior validation process. In our knowledge, no validated scale exists for evaluating exit site of HD-CVC.

Current clinical practice guidelines on vascular access for haemodialysis and infection control do not provide a universal definition regarding exit site infection [1,18,22–24]. In this respect,

the 2019 update of the KDOQI Clinical Practice Guideline [22] indicates as a recommended area for future research "further validation studies of diagnostic criteria for exit site and tunnel infections in haemodialysis patients".

Therefore, we consider it necessary and timely to design and validate a scale for assessing the exit site of tunneled HD-CVC that underpins the recommendations of clinical practice guidelines.

The EXIT site Assessment (EXITA) study's primary objective is to validate a clinical scale for the exit site assessment of tunnelled HD-CVC to reduce infections in patients on haemodialysis in Spanish hospitals. The secondary objectives are: 1) To evaluate the incidence of infectious complications in the exit site of HD-CVCs and their risk factors; and 2) To determine the relationship between the variability of the exit site care by healthcare professionals and the incidence of ESI.

Methods and analysis

Design

The EXITA study is intended to validate an instrument for the early detection of ESI in tunnelled HD-CVCs. The scale development will consist of two phases:

1. Scale design. After identifying the clinical signs and symptoms, by a scoping review of the literature, they will be categorised by an international panel of experts in HD-CVC exit site care, using the Delphi technique. The Delphi protocol has been published recently [35]. The prioritisation thus obtained will be used to develop the preliminary version of the assessment scale we propose.

2. Validation. We will conduct a prospective cohort study in a population of patients who have a HD-CVC, differentiating between those presenting ESI and those who are free of infection.

Timeline for the study

Pilot study with scale version 1 will take place in May 2021. Patients' recruitment take place during validation study period: this period will be from 1 May 2021 to 30 June 2022. Data analysis, the review of the behavior of the items of the scale and its version 2, are scheduled to take place in May-June 2022, after reaching the planned sample size. Data analysis and report Timeline of EXITA study is presented in figure 1.

Setting

This version of the assessment scale will then be subjected to a pilot and validation study with patients on haemodialysis in seven regions (Autonomous Communities) of the decentralised Spanish health system at the following hospitals: Marqués de Valdecilla University Hospital, Alcorcón Hospital Foundation, Gregorio Marañón University General Hospital, Manacor Hospital, Navarra Hospital Complex, University Clinical Hospital of Valladolid, University Hospital of the Canary Islands, Reina Sofía University Hospital of Córdoba and Quironsalud Hospital of A Coruña.

Subjects

The following inclusion criteria will be applied: patients with a tunnelled CVC one month after insertion (when the catheter is considered stable), undergoing renal replacement therapy with haemodialysis, aged at least 18 years, who consent to participate in the study. Patients who, due to their clinical and/or personal situation, cannot consent to participate will be excluded.

Sample size

The minimum sample size was calculated taking as a reference a mean ESI incidence around 20% in Spain [36–38], with an expected sensitivity of 95% and an expected specificity of 90%. Due to there are no validation studies of similar scales in vascular catheters (neither peripheral

nor central), these expected properties are based on Eriguchi et al. results in the validation of the exit-site scoring system for peritoneal dialysis catheter, recommended by the 2005 guidelines of the International Society for Peritoneal Dialysis [39]. We calculate that 92 patients should be included in the ESI group in order to estimate the presence of exit site infection, with 95% confidence level and a precision of ±10 percentage units. Similarly, 365 patients should be included in the non-ESI group in order to estimate, with 95% confidence level and a precision of ±5 percentage units. Sample size was calculated using Epidat 4.2™ software [40].

Data collection

The first version of the scale will be piloted in ten patients at each participating hospital, assessed by three nurses in each case. This initial approach is intended to obtain a linguistic validation of the instrument and thus assess its understandability and clarity. In addition, a qualitative analysis will be performed of the opinions expressed and according to the results obtained, the scale will be modified as appropriate, to produce the definitive assessment instrument.

This final version will then be taken as the exit site assessment method to be applied before each haemodialysis session at the participating hospitals (where the exit site treatment protocol will remain unchanged). A record will be kept of the data thus obtained, including clinical and catheter-related variables. If the patient presents more than one HD-CVC during the study period, the corresponding data will be collected for each catheter. For every HD-CVC, an initial control culture will be obtained, based on a pericatheter skin smear from a healthy exit site (i.e., with no signs or symptoms of infection). During each haemodialysis session, the absence or presence of each item will be assessed. Nurses of the participating centers will receive training for the unequivocal identification of the signs/symptoms to be validated in order to eliminate observer bias. If any item is present, a microbiological study of pericatheter skin smears and/or

exit site exudate will be carried out. A pericatheter skin swab culture will be repeated when the signs/symptoms disappear. For samples a dry cotton swab will be rubbed over a 2-cm^2 area around the insertion site, immediately after dressing removal, without performing skin disinfection [1,23]. Exclusion criteria to collect pericatheter skin smears: presence of local allergic reaction and /or bleeding. Data related to the microbiological study will be collected (Table 1).

HD-CVC ESI will be diagnose when the pericatheter skin smears and/or exit site exudate culture be positive (≥15 CFU/ml by semiquantitative Maki's technique or ≥1,000 CFU/ml by Cleri´s technique) [1,23]. Skin contamination will not be considered infection and not be included in statistical analysis.

At each participating hospital, the local protocols applied regarding HD-CVC maintenance and the management/treatment of related infections, both local and systemic, will remain unchanged. The proposed assessment scale will continue to be applied until the necessary sample size is reached among the participating hospitals (within an estimated 8-12 months).

Variables and definitions

Table 1 shows the variables to be considered and their definitions.

Table 1. Variables and definitions

Group	Variable	Definition
Clinical variables	Age (continuous quantitative)	Years (n)
	Sex (qualitative)	Male Female
	Kidney disease aetiology (qualitative)	According to the ERA/EDTA coding
	Degree of comorbidity (qualitative)	According to the Modified Charlson Index for patients with kidney failure

	Months in kidney replacement therapy with hemodialysis (quantitative)	Months (n)
Catheter-related variables	Catheter design (qualitative)	One exit site Two exit sites
	Duration of catheter insertion (quantitative)	Days elapsed since the insertion
	Venous insertion (qualitative)	Subclavian (left or right) Jugular (left or right) Other
	Previous CVC-related infections (qualitative)	Exit site infection: Yes / No Tunnel infection: Yes / No Bacteraemia: Yes / No
Variables related to local CVC maintenance	Frequency of dressing change (qualitative)	At each dialysis session Weekly As required Other frequency
	Antiseptic (qualitative)	Chlorhexidine aqueous solution 0.5% Chlorhexidine alcohol solution 2% Povidone iodine Alcohol 70% Other antiseptic Antibiotic instillation
	Dressing (qualitative)	Gauze Partially reinforced transparent polyurethane Fully reinforced transparent polyurethane Transparent polyurethane with chlorhexidine gluconate window Other
	Frequency of ES evaluation (qualitative)	At each dialysis session Weekly As necessary Other
Variables concerning catheter-related infections during follow-up	Presence of scale items (qualitative/ quantitative)	Yes= 1 point No= 0 points
	Culture (qualitative)	Type of sample collected (pericatheter smear and/or exudate), culture method, result (including microorganisms if positive culture).

Data analysis

To validate the scale, a logistic regression analysis will be performed. To select the signs/symptoms of the scale in the multivariate analysis, a univariate analysis will be carried out with each sign/symptom, following the selection criteria proposed by Hosmer, Lemeshow

and Sturdivant [41], in which variables with a level of significance less than 0.25 will be considered. In addition, the clinical relevance of the signs/symptoms will be considered, regardless of the statistical significance. Using logistic regression, the β coefficients of each of the signs/symptoms of the scale to be validated will be estimated. Later, we will use the formula:

$$\text{Logit ESI} = \text{constant} + \beta_1 \times X_i + \ldots \beta_n \times X_n.$$

To transform the logit ESI into ESI probabilities, the following formula will be used:

$$\text{ESI probability} = e^{\text{logit ESI}} / 1 + e^{\text{logit ESI}}$$

In this way we will obtain the probabilities, expressed as a percentage, that a patient with a HD-CVC has of presenting OS infection [41,42].

To address the secondary aims of this study, a descriptive analysis of the variables will be performed, including the distribution of the phenomena under study within each of the dialysis units concerned. A multiple regression analysis will be carried out to determine the association between the presence of infectious complications (as determined by microbiological tests) and the clinical variables, catheter-related variables and local catheter maintenance policies. Statistical analysis will be performed using SPSS software (version 20.0) and MedCalc software (version 19.6).

Patient and public involvement

None.

Ethics and dissemination

The study will not involve any clinical intervention or change in usual practice. The patients concerned will be asked by the clinician nurse to provide signed informed consent and will be given clear written information about the purposes and implications of the research. The computerised database will not contain patient identification data. The individuals involved in

compiling the data will sign a confidentiality agreement. The Research Ethics Committee with Medical Products of Cantabria (CEIm of Cantabria, approval code 2019.146) has approved this protocol study. We will send the findings of this study to a peer-reviewed scientific journal for publication.

Discussion

Using a validated instrument to assess the exit site of the HD-CVC will make observations more objective, facilitate a uniform classification and thus enable results to be readily compared. The use of a validated exit site assessment scale can reduce the likelihood of local and systemic infectious complications in patients on haemodialysis, reducing morbidity, hospitalizations, mortality and associated costs. Moreover, its use will provide continuity of care and a documented record of exit site evolution. This instrument will also help researchers achieve a uniform measure of the effects of interventions on the incidence of ESI complications. Finally, this instrument will enable patients to receive objective information about the status of the catheter exit site, accustoming them to identify signs of infection at an early stage and fostering self-care.

Mapping clinical variability in issues related to maintaining the exit site, as proposed in this study, will provide valuable support for future research into the implementation of evidence-based measures.

One limitation of the study is that each patient included may present one or multiple episodes of HD-CVC ESI without being able to formally verify that the different episodes from a single patient are independent of each other. The study will be carried out in nine hospitals of seven regions of the decentralised public health system in Spain, to maximise the external validity of the scale to be developed. However, this multicentre approach will also influence clinical variability, in terms of CVC maintenance and the treatment approach adopted to local

infections. A protocol on collecting samples for microbiological culture has been designed with the aim of avoiding bias.

Contributors: JLCS coordinates the research team and is responsible for reporting to Ethics Committees and every institution involved in the study. JLCS and IBM revised previous literature on haemodialysis CVC guidelines and recommendations and previous ES assessment scales. JLCS, IBM and JEPG designed the scale design and data collection methods, together with NMS, RPA and IFF. JLCS, IBM and JEPG audited the study design, especially concerning the proposed statistical analysis. JLCS, IBM and JEPG wrote the first version of the protocol, which was later edited by all the authors.

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Competing interests: None declared.

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Figure title

Figure 1. EXITA study timeline

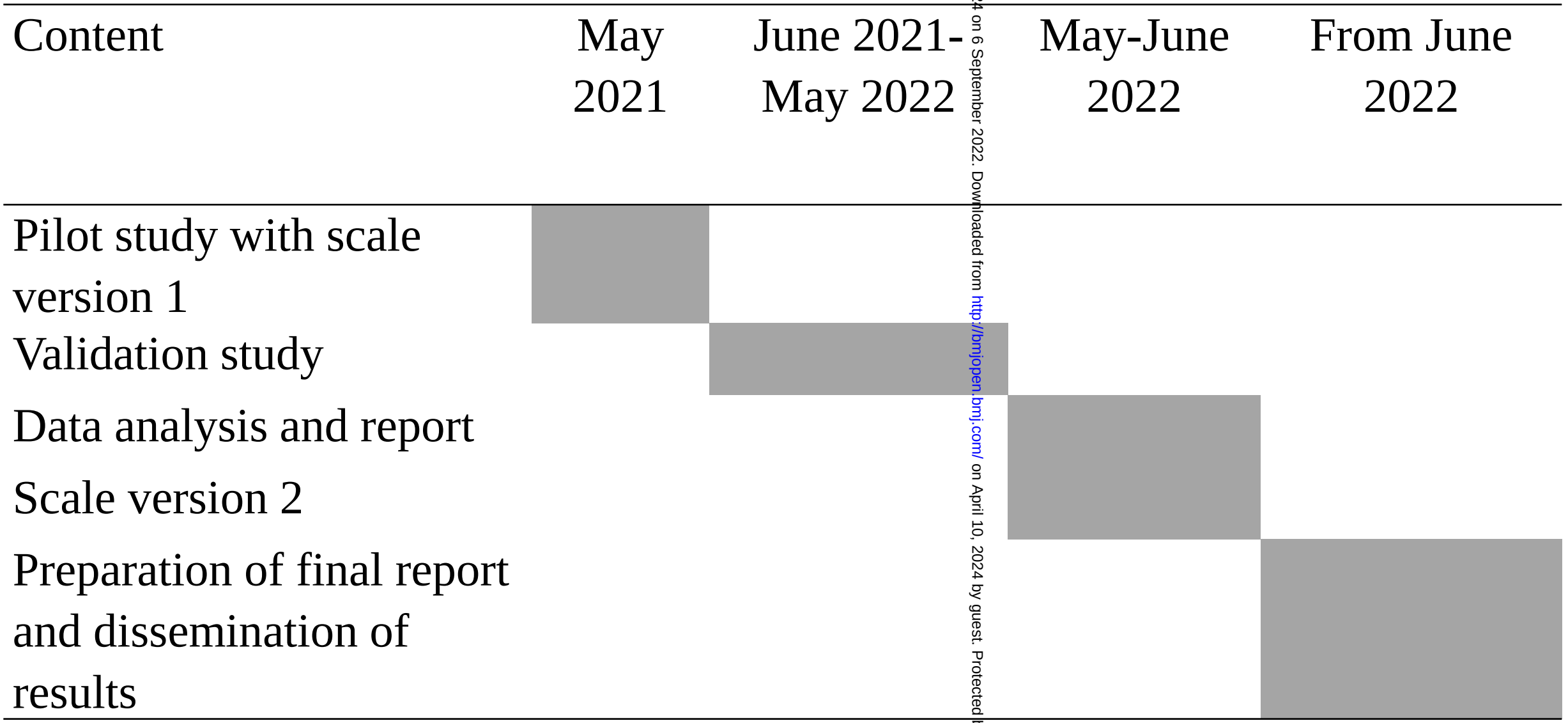

Figure 1.- Timeline of EXITA study.