Study Protocol and Statistical Analysis Plan

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Electronic Device Implantation Through Remote Guidance

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List of Abbreviations

- CRP: C-reactive protein
- CRT-D: Cardiac Resynchronization Therapy with Defibrillator
- CT: Computed Tomography
- ECG: Electrocardiogram
- EP: Electrophysiology
- EU: European Union
- FCS: Field Clinical Specialist
- HF: Heart Failure
- ICD: Implantable Cardioverter-Defibrillator
- IQR: Interquartile Range
- INR: International Normalized Ratio
- LVEF: Left Ventricular Ejection Fraction
- NYHA: New York Heart Association
- RM: Remote Monitoring
- SCD: Sudden Cardiac Death
- SD: Standard Deviation
- S-ICD: Subcutaneous Implantable Cardioverter-Defibrillator
- TV-ICD: Transvenous ICD

1. Introduction

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide, with sudden cardiac death (SCD) and heart failure (HF) representing major clinical and economic burdens. Implantable Cardioverter Defibrillators (ICDs) and Cardiac Resynchronization Therapy with Defibrillator (CRT-D) devices are evidence-based therapies that have significantly improved survival in patients with systolic dysfunction and electrical dyssynchrony.

The standard practice of device implantation relies heavily on the presence of a Field Clinical Specialist (FCS), a biomedical engineer who provides intraoperative technical support. However, the physical presence of FCS personnel is not always feasible, especially in rural areas or during public health emergencies such as the COVID-19 pandemic. In this context, telemedicine represents a potentially transformative approach to decentralize technical expertise and make advanced cardiac care more accessible.

This protocol describes a structured, stepwise investigation to assess whether remote FCS guidance can safely and effectively substitute the in-person presence during ICD and CRT-D implantation procedures.

2. Background and Rationale

The implantation of ICD and CRT-D devices involves complex decision-making and precise programming of leads and generators, for which collaboration between electrophysiologists and FCS personnel is considered standard of care. Remote monitoring (RM) of implanted devices has already demonstrated safety, efficiency, and improved clinical outcomes post-discharge. However, little is known about the application of telemedicine during the implantation phase.

This knowledge gap is particularly significant in healthcare systems with limited resources or geographic barriers, where the availability of expert personnel cannot be always guaranteed. Telemedicine systems that enable real-time audiovisual communication, device programming, and procedural support may offer a safe, cost-effective alternative, but require formal validation.

In this study, we propose a three-phase approach, including preclinical simulation, phantom testing, and randomized controlled patient enrollment, to evaluate the feasibility and safety of remotely guided ICD/CRT-D implantation.

3. Objectives

- To evaluate the feasibility and procedural success rate of ICD and CRT-D implantations performed under real-time remote guidance by a FCS.
    - To assess differences in total EP lab occupancy time (minutes).
    - To compare fluoroscopy time (minutes) as a marker of radiation exposure.

- To evaluate the technical stability of implanted device parameters (voltage, impedance, amplitude).
- To document any procedural complications or need for reintervention.

4. Study Design

This is a prospective, randomized, controlled pilot study with a 2:1 allocation ratio. After initial validation phases (simulator and phantom), thirty patients will be randomized to:

- **Control group**: Standard implantation with FCS physically present in the EP lab.
- **Intervention group**: Implantation conducted with the FCS providing remote audiovisual guidance.

Randomization will be stratified by device type (ICD, CRT-D, S-ICD) to ensure balance between groups.

5. Study Population

Patients scheduled for ICD or CRT-D implantation at the Cardiology Units of the Academic Hospital "Annunziata" in Cosenza and Academic Hospital "Renato-Dulbecco" in Catanzaro will be screened. All participants will be asked to sign informed consent prior to inclusion.

6. Inclusion and Exclusion Criteria

Inclusion Criteria:

- Age: 18–85 years.
- Indication for de novo ICD or CRT-D implantation according to ESC Guidelines.
    - Primary prevention of SCD with LVEF ≤ 35% (measured by echocardiography, Simpson biplane method) and NYHA class II or III, on optimal medical therapy for at least 3 months.
    - Secondary prevention in survivors of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia.
    - Indication for CRT-D: LVEF ≤ 35%, QRS duration ≥ 130 ms, preferably with left bundle branch block morphology, and NYHA II–IV symptoms.
- Written informed consent signed.

Exclusion Criteria:

- Permanent pacemaker dependency requiring tailored programming strategies.
- Previous device implant with generator replacement only.

- Active infection or systemic inflammation defined by the presence of at least one of the following:
    - C-reactive protein (CRP) >10 mg/L
    - Body temperature >37.5°C
    - Clinical signs of systemic inflammation (e.g., leukocytosis >12,000/mm^3 or leukopenia <4,000/mm^3)
    - Suspected or confirmed sepsis as per Sepsis-3 criteria: an increase in SOFA score ≥2 points from baseline and confirmed or suspected infection, supported by imaging (e.g., pulmonary infiltrates on chest X-ray, abscess on ultrasound/CT) or microbiological tests.
- Participation in other investigational studies that may interfere with this protocol.
- Pregnancy or lactation.
- Cognitive or psychiatric impairment interfering with consent or adherence.
- Severe coagulopathy (INR >2.5 without correctable cause).

7. Intervention and Procedures

Each procedure will follow the standard protocol for device implantation. In the control arm, the FCS will operate in person, while in the intervention arm, the FCS will be connected through a secured video/audio system using high-definition PTZ cameras, screen sharing from the programmer, and real-time communication.

Procedural steps include:

- Venous access (usually via left or right subclavian or cephalic vein).
- Lead positioning under fluoroscopic guidance.
- Intraoperative testing: pacing threshold (V), sensing amplitude (mV), impedance (Ohm).
- Generator placement and programming.
- Wound closure and sterile dressing.

Total EP lab occupancy time and skin-to-skin procedural duration will be recorded.

8. Data Collection and Management

A case report form (CRF) will be compiled for each participant. Collected data include:

- Demographics, clinical history, and indication for implantation.

- Intraoperative data: lead model, positioning, parameter values (e.g., ventricular threshold in V, impedance in Ohm).
- Adverse events and complications.
- Remote monitoring reports at 1 and 6 months.

Data will be pseudonymized and stored in a secure, password-protected database. Data protection will comply with GDPR and institutional guidelines.

9. Outcome Measures:

- **Procedural success:** defined as completion of the device implantation with acceptable electrical parameters:
    - Atrial threshold <1.0 V at 0.5 ms pulse width
    - Right ventricular threshold <1.0 V at 0.5 ms
    - Atrial sensing >1.0 mV; ventricular sensing >5.0 mV
    - Lead impedance 300–1500 Ohm
    - LV threshold (for CRT-D) <2.5 V at 0.5 ms with confirmed biventricular pacing on ECG
- EP lab occupancy time: measured in minutes from patient entry to exit.
- Fluoroscopy time: total duration in minutes of x-ray exposure during the implantation.
- **Procedural complications:**
    - Lead dislodgement confirmed by chest x-ray or electrical changes
    - Pocket hematoma requiring intervention
    - Infection requiring antibiotic therapy or reintervention
    - Generator malfunction
- **Parameter stability at follow-up:**
    - Variation in pacing thresholds, impedance, and sensing values over time
    - Defined as Δ parameter < ±20% from baseline
- **Remote monitoring performance:**
    - Number of successful data transmissions

- Device alerts and clinical actions triggered

10. Statistical Analysis Plan

The statistical analysis of this pilot study is designed to explore the feasibility and preliminary outcomes associated with remote versus standard FCS-guided ICD/CRT-D implantation. All data will be analyzed using IBM SPSS Statistics version 23.0.

Descriptive statistics will be used to summarize the overall sample characteristics. Continuous variables (e.g., fluoroscopy time, procedural duration, electrical parameters) will be described using means and standard deviations (SD) if normally distributed, or medians and interquartile ranges (IQR) otherwise. Categorical variables (e.g., procedural success, complications) will be reported as absolute frequencies and percentages.

Normality of continuous variables will be assessed with the Shapiro–Wilk test. Homogeneity of variances will be verified using Levene's test.

For group comparisons:

- Unpaired Student's t-test will be used for continuous variables with normal distribution.
- Mann–Whitney U test will be used for non-normally distributed continuous variables.
- Chi-square test or Fisher's exact test will be applied for categorical variables, depending on expected frequencies.

In addition, longitudinal evaluation of device parameters (e.g., thresholds and impedances) from baseline to follow-up (1 and 6 months) will be analyzed using repeated measures ANOVA for normally distributed variables or the Friedman test for non-parametric distributions.

To enhance the robustness of findings, particularly given the limited sample size, bootstrap resampling with 5,000 iterations will be used to generate empirical confidence intervals (95% CI) around key estimates.

A two-sided p-value <0.05 will be considered statistically significant. Effect sizes (e.g., Cohen's d or rank biserial correlation) will be reported where appropriate to aid interpretation.

Missing data will be handled through complete-case analysis. If the rate of missingness exceeds 5% for any primary variable, a sensitivity analysis will be performed using multiple imputation to explore the potential impact on results.

All analyses will be exploratory in nature given the pilot status of the trial, and the results will be used to inform sample size calculations for future larger-scale studies.

11. Ethical and Regulatory Considerations

The protocol has been reviewed and approved by the institutional ethics board. All participants will sign an informed consent form. The study adheres to the Declaration of Helsinki and Regulation EU 679/2016.

12. Risk Management

The technical risk is minimized by preclinical testing and in-hospital presence of the FCS, even in remote procedures. All personnel are trained. Backup systems (local programmers, redundant connections) are in place. Defibrillation testing will only occur in patients where clinically indicated and with on-site FCS.

13. Dissemination Plan

Results will be submitted to peer-reviewed journals. Participants will be offered a summary of the findings on request**.**