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# Multicenter oncology clinical trials in primary health care in Cuba: evaluation of program implementation in Villa Clara Province, 2010-2020

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**Abstract**

**Background:** The Center of Molecular Immunology of Cuba has developed a program for the conduction of multicenter oncology clinical trials in primary health care centres since 2009. **Aim:** To evaluate the ability to conduct oncology clinical trials in primary health care **Design and Setting:** A longitudinal, prospective, analytical study was developed between July 2010 and August 2020 in the Villa Clara province. **Methods:** Structure, process, and outcome indicators were evaluated by the methods of a structured interview, direct observation, documentary observation and databases analysis. The investigators' curricula vitae, the Investigator Site File, minutes of workshops, the monitoring reports, the clinical trial training records and databases were employed as sources of information. The following criteria were considered: a*dequate:* when the indicator met the standard and *not adequate:* when the indicator did not meet the standard. **Results:** The six structure indicators reached *adequate results* and showed that the program has allowed building of capacities to conduct clinical trials in primary care. The eight processes indicators and two outcome indicators were considered *adequate* too. Trials conducted in primary care showed better indicators of patient recruitment than secondary care. Both scenarios showed similar behaviour for the process indicators: retention, protocol compliance and safety. Survival and satisfaction with health services were also

comparable in both scenarios **Conclusions**: The evaluation of the program showed adequate indicators for conducting oncology clinical trials in primary care in Villa Clara and these were comparable to those determined in the secondary care.

**Keywords:** clinical trials, primary health care, oncology, immunotherapy

**How this fits in**

Oncology clinical trials are mainly developed in specialized medical care centers. The Center for Molecular Immunology of Cuba has developed immunotherapies for the treatment of cancer, with proven safety and efficacy in previous Phase I, II, and III studies, developed in hospitals. The safety profile of these products allows their use in primary care institutions, so scientific evaluation is necessary for this context through clinical trials, to allow their subsequent introduction as part of routine medical practice.

## INTRODUCTION

A few years ago, the life expectancy of cancer patients was very limited, but in recent decades this picture has changed and for some types of cancer prolonged survival rates are observed, reflecting the combined effects of earlier diagnosis, new treatments, and better care[1]. Advances in personalized medicine and immuno-oncology have demonstrated therapeutic efficacy in several types of cancer and, at the same time, lower toxicity than classical cytostatics, characteristics that allow the use of these therapies for long periods, even beyond disease progression [2, 3]. These two elements have indicated the need to pay greater attention to the follow-up of cancer patients in primary health care (PHC), an ideal setting for the care of chronic patients [4, 5]. In addition, research conducted in this setting is becoming more relevant, allowing studies that recruit a "real-world" patient population that is not well represented in clinical studies conducted under controlled hospital conditions [5].

The Center for Molecular Immunology, in Havana, Cuba, has developed several innovative immunotherapies for the treatment of cancer. These innovative molecules have demonstrated their efficacy and safety in phase I, II, and III clinical trials, developed in hospitals across the whole country and abroad. The optimal use of these products

implies repeated doses and prolonged administration. These elements made us think about the possibility of administering these therapies in the primary health care setting [6, 7]. The first experience in the country began with clinical trials in PHC with the CIMAvax-EGF vaccine, registered for the treatment of adult patients with advanced lung cancer [8, 9]. Its treatment scheme comprises 4 induction doses administered every 14 days and subsequently, maintenance doses every 28 days until the patient's clinical conditions allow it [10, 11].

In Cuba, there was no previous experience in conducting clinical trials (CT) with products for cancer treatment in PHC centers, so it was necessary to design and implement a clinical trial program adapted to the conditions of this scenario.

The aims of the present work were to evaluate the ability to conduct oncology clinical trials in PHC, based on the experience of the CIMAvax-EGF vaccine in Villa Clara province.

## METHOD

### Population

The central Cuban province of Villa Clara is composed of 13 municipalities and had a population of 777 500 inhabitants with a population density of 92.4 inhabitants per km2 in 201912. Malignant tumours were the second leading cause of death this year with 1 696 deaths and a rate of 218.2 per 100 000 inhabitants. Specifically, trachea, bronchus, and lung tumours ranked first in mortality with 5 626 deaths this year13.

The oncology services are provided at the "Celestino Hernández Robau" Hospital, which provides regional services to the provinces of Villa Clara, Cienfuegos, and Sancti Spíritus and supervise an estimated population of 2.9 million inhabitants.

The province has 37 primary care units called "polyclinics" in 18 municipalities; clinics belonging to the primary care system that concentrate services of the main medical specialties and are located in each Cuban community, whose main objective is to provide comprehensive health service to all inhabitants. Villa Clara has 7,499 physicians, which represents 9.65 per 1,000 inhabitants and 1753 of them are general practitioners located in the community[13].

**Study design and data sources**

A longitudinal, prospective, analytical study was developed between July 2010 and August 2020, during conducting two open-label, uncontrolled, non-randomized, multicenter, Phase IV clinical trials. These trials were carried out to evaluate the CIMAvax-EGF vaccine in PHC institutions and were registered in the National Public Registry of Clinical Trials http://www.who.int/ictrp/network/rpcec/en with trials numbers RPCEC00000181 (secondary identifying number IIC RD-EC-120) and RPCEC00000205 (secondary identifying number IIC RD-EC-157), respectively. Trial number IIC RD-EC-157 is still ongoing, so, the database cut-off was performed on August 31, 2020.

The first trial is a pilot experience in 6 polyclinics in the municipality of Santa Clara, the capital area of the province. The second trial expanded the program to the entire province and covered 17 polyclinics. This trial incorporated the evaluation of EGF concentration as a predictive biomarker of therapeutic success with the CIMAvax-EGF vaccine.

Qualitative and quantitative methods were used to evaluate the program. The structure, process, and outcome indicators, as well as the instruments used in the evaluation for the collection of information and their comparative standards, were previously validated through expert consensus using the Delphi modification methodology 14, 15. An exhaustive content analysis of all documents produced by the different institutions and actors involved in the clinical trials was analyzed. These comprised the investigators' curricula vitae, the Investigator Site File (ISF), minutes of workshops, the trial monitoring reports, and the provincial clinical trial training records.

Structural indicators include infrastructure, material, and human resources used in the conduct of clinical trials. Process indicators examined whether the clinical trial program was conducted as planned. The outcome indicators were designed to assess the effects of the program on the patients' health status (Survival) and the degree of patient satisfaction with the care received (Supplementary Table 1).

For “survival”, the databases of the clinical trials were used. Patients with non-small cell lung cancer verified by histology or cytology, stage IIIB or IV, performance status 0-2, stable disease, or response to first line oncology treatment were included in the analysis.

The indicator “Satisfaction with health care” was evaluated in this subset of patients. The instrument used was the IN-PATSAT32 questionnaire from the European Organization for

Research and Treatment of Cancer (EORTC)16. The questionnaires were applied to the patients, 3 months after the beginning of the treatment with the immunotherapy by the psychologist of the investigational team, prior informed consent of the patient. Question number 21 was omitted because it was not applicable in this context. For this indicator, a cross-sectional comparison was made with patients included in clinical trials with CIMAvax-EGF in the hospital, in the same period.

For the evaluation of the program implementation, the indicators were compared with the comparative standards validated by experts. The following criteria were considered: adequate: when the indicator met the standard and not adequate: when the indicator did not meet the standard (Supplementary Table 1).

Additionally, the results were compared with the indicators obtained in the previous CIMAvax-EGF open-label, controlled, randomized, Phase III trial conducted in the hospital (RPCEC00000161, secondary identifying number IIC RD-EC081) considered as historical control (external and non-concurrent). The general scheme of the study was shown in Supplementary Figure 1.

**Statistical analysis**

All Villa Clara patients included in the databases of each trial were considered. The SPSS version 19 program was used. The process and outcome indicators were calculated considering the formula defined for each one (Supplementary Table 1).To evaluate overall survival the primary variable was the survival time measured from the date of the inclusion in the trial to the date of death of the patients or the date of the latest news. Survival times of all patients were estimated using the non-parametric Kaplan-Meier estimator. Median survival and its confidence intervals were estimated. Survival curves between trials were compared using Log rank two-tailed test, considering a significance level of $p = 0.05$.

For “Satisfaction with Care” analysis, the mean and standard deviation were calculated and comparisons using t-Test for independent samples were made. A level of statistical significance of $p=0.05$ was considered.

## RESULTS

### Structure indicators

For the five structure indicators, the evaluation of *not adequate* was obtained during the conduct of the first clinical trial protocol (IIC RD-EC-120) developed in the period 2010-2015. These were worse than the proposed standard for the creation of capacities for conducting clinical trials in 90% of the municipalities of the province. However, the indicator "percentage of professionals and technicians trained in clinical trials and oncology" obtained the qualification *adequate* (Table 1).

For the second protocol (IIC RD-EC-157), the six indicators showed *adequate* results, reaching 90% of the municipalities in the province incorporated into the program and 100% of the human resources trained. In addition, the implementation of electronic data management and Standard Operating Procedures adapted to PHC institutions is highlighted (Table 1). The results showed the expansion of the program and the continuous improvement of the implementation process.

### Process indicators

The centralized Ethics Committees allowed obtaining approval time for the protocol and its modifications in less than 30 days, similar to those achieved in secondary care (Table 2).

For the "province recruitment vs total trial recruitment" indicator, a proportion of 17.2% was obtained for the studies conducted in PHC vs 5.8% for the trial conducted in the hospital. Likewise, the "proportion of recruited patients in relation to the incidence of the disease" was higher in the trials conducted in PHC with 14.6 % compared with SHC, where only 2% was found. The same behaviour was obtained for the indicator "inclusion rate" where an increase from 0.36% in SHC to 4.0% in PHC was observed (Table 2).

The "percentage of randomized participants who have withdrawn consent to continue in the study" indicator showed similar results in both scenarios, with values of 10.3% and 9.6% for SHC and PHC, respectively. In the same way, adherence was similar too, with percentages of 6.8% and 5.4% of non-compliance with the treatment scheme for secondary and primary care, respectively (Table 2).

For the indicator “number of grade 3-4 related adverse events per number of randomized participants”, in PHC units 1.9% was determined vs 6.0% in SHC. Likewise, the “percentage of related serious adverse events” was lower for the trials conducted in PHC (2.5%) than in the trial conducted in SHC which 6.0% was determined. All identified adverse events were consistent with those found in previous trials (Table 2).

The eight process indicators in PHC met the comparative standard, for which they were evaluated as *Adequate* (Table 2).

**Outcome indicators**

Median survival of 10.46 (8.44 - 12.48) and 9.86 (7.11 - 12.62) respectively, were obtained for the trials conducted in the PHC (ICC RD-EC120 and ICC RD-EC-157), which were similar (p = 0.907) to the median of 10.40 (4.85 - 15.94) found in the previous Phase III CT conducted in the hospital (ICC RD-EC081). The 12-month survival rates were 43.1 and 44.0 for the CTs conducted in the PHC and 44.6 for the CT conducted in the hospital, which were also comparable.

For the 2010-2015 period, the general indices of satisfaction with care were 91.8 ± 9.5 for PHC centres vs 96.0 ± 3.2 for SHC, showing statistically significant differences (p = 0.02); however, the values are above 80 points, which are classified as *adequate.*

In the 2016-2020 period, these values were higher than the previous period and without statistically significant differences (p = 0.07). For PHC centres, values of 94.4 ± 8.0 were determined vs 97.9 ± 1.5 for SHC.

The two outcome indicators also met the comparative standard and were assessed as *Adequate* (Table 2).

## DISCUSSION

**Summary**

This is the first study in Cuba that evaluates indicators of structure, process, and outcome in the implementation of a program for conducting clinical oncology trials in primary health care centres. Our results provide novel data on the feasibility of its implementation.

Structure indicators showed that the program granted the adequate infrastructure, as well as the material and human resources required to meet the international quality standards required for these investigations [17-20].

Processes indicators reached comparable values to those obtained in Phase III randomized CT developed in the hospital for the domains: ethical approval, patient retention, protocol compliance, and safety. Regarding the patient recruitment indicators, the study showed that the PHC facilitated the recruitment of a greater number of patients in a shorter period of time, and the inclusion rates were greater than those achieved in SHC. Similarly, greater coverage of treated patients was achieved by reaching high proportions of patients treated in relation to the incidence of the disease.

In our research, the survivals achieved for patients who received the product in primary and secondary health care were similar. This indicator tested in the group of patients who met the same inclusion criteria guaranteed that the only difference was the level of medical care at which the patient was cared for. On the other hand, "satisfaction with health care" was also comparable for patients enrolled in CT in PHC and SHC, obtaining high levels of satisfaction in both scenarios. In conclusion, these findings suggest that patients followed in the hospital by the oncologist showed survival and levels of satisfaction similar to those followed by the general practitioners in PHC together with the oncologist.

Our experience also suggested that the PHC setting was adequate for the implementation of pragmatic clinical trials [21], with protocols with less stringent inclusion criteria [22] that combine simple variables that can be determined in PHC centres, with others, that can be evaluated in SHC. To achieve this goal, a satisfactory integration between these levels of care, are needed.

**Strengths and limitations**

The main strength is that this longitudinal study used data spanning 10 years and included 17.2% of the total patients enrolled in the CT.

There are some limitations. The CT used as an external control was developed in an earlier period and a different setting, so the uptake indicators may have biases due to the different conditions in which it was carried out.

On the other hand, satisfaction with services in the CT carried out at PHC could not be compared with the external control, because this aspect was not evaluated for a trial conducted at the hospital level. For this aspect, only the cross-sectional comparison was performed.

**Comparison with existing literature**

Few references were found of programs for conducting oncology clinical trials in PHC. Ersek J et al published considerations on critical aspects to consider for the sustainability of a research program based on oncology practices in the community. This study describes only the basic elements of the program but does not declare indicators for its evaluation. Our work is in line with the basic elements described by these authors [5], but it also proposes and evaluates feasibility indicators for the program implementation. These indicators are representative of the fundamental aspects contained in the main international and national guidelines that regulate the conduct of clinical trials [18-20].

The process indicators are consistent with those defined by Whitham D. et al in a study that validated indicators for the monitoring of multicenter randomized clinical trials using the Delphi methodology [23]. Our study also defines indicators for the evaluation of processes and outcomes, using the Donabedian framework of Structure-Process-Outcome recommended for the evaluation of real-world health interventions[14].

The results obtained in our study for the process indicators agree with those reported by other authors. The time for ethical approval of the protocol and modifications met the standard established by international regulations [19, 20, 24]. It was determined that the incorporation of PHC into the trials can facilitate the recruitment of a greater number of patients, similar to that reported by Orzano J et al [25]. On the other hand, the rate of lung cancer patients enrolled in the trials, in relation to the incidence of the disease (14.3%), was higher than this indicator in the Netherlands (7.6%) [26]. Besides, the evidence of product safety in the PHC setting and real-world conditions were consistent with findings from the previous Phase III trial conducted in hospitals[27].

Similarly, the high levels of satisfaction with services obtained in both settings are similar to those obtained by Grundfeld E et al. in a randomized trial comparing the satisfaction of breast cancer patients followed in specialized institutions versus primary care. The study showed that some patients prefer to be followed in a setting close to their home, work, and family[28].

Our program promotes protocols in line with the "shared model" proposed by American and European oncology societies, which include an initial intensive follow-up of the patient in the hospital for first-line oncology treatment, and then the patient is transferred to the PHC to receive immunotherapy; maintaining periodic quarterly visits to the hospital [29].

**Implications for practice**

The program has enabled the participation of cancer patients in clinical trials conducted in their municipality of residence, facilitating better access to treatment with good adherence to the protocol.

It has also prepared the healthcare system for the administration of new therapies as part of routine medical practice, building capacity and implementing work standards and routines to be used in this routine practice. On the other hand, it will allow the implementation of other complex health interventions [30].

**Conflict of Interest Statement**

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Table 1.** Indicators of structure in the conduction of multicenter oncology clinical trials in primary care institutions. Villa Clara province, 2010-2020.

| Indicators | Structure indicators | | | |
|---|---|---|---|---|
| | **2010-2015 period Clinical Trial ICC RD-EC120** | **Evaluation** | **2016-2020 period Clinical Trial ICC RD-EC-157** | **Evaluation** |
| **1. Percentage of polyclinics conditioned to conduct clinical trials in the province** | **33 % (6/18)** (6 clinical trials consultation, 6 locals for product administration, 6 pharmacies, 6 laboratories) Certification of compliance of Good Clinical Practices (GCP) | **Not adequate** (<90%) | **94 % (17/18)** (17clinical trials consultation, 17 local for product administration, 17 pharmacies, 17 laboratories) Certification of compliance of Good Clinical Practices (GCP) | **Adequate** (>90%) |
| **2.Percentage of municipalities participating in the clinical trials program** | **76 % (1/13)** | **Not adequate** (<90%) | **92 % (12/13**) | **Adequate** (>90%) |
| **3. Percentage of completed investigation teams** | **33% (6/18)** clinical research teams composed by : 6 primary care physicians, 6 nurses, 6 pharmacist, 6 specialist in Laboratory, 6 psychologists | **Not adequate** (<90%) | **94% (17/18)** clinical research teams composed by: 17 primary care physicians, 17 nurses, 17 pharmacist, 17 specialist in Laboratory, 17 psychologists | **Adequate** (>90%) |
| **4. Percent of professionals and technicians trained in clinical trials and oncology** | **100% (337/337)** Courses of Good Clinical Practices, Adverse Events, Pharmacy, Clinical Laboratory, Nursing 83 general practitioners trained in oncology (37 general doctors, 37 nurses and 9 other professionals) | **Adequate** (100%) | **100% (373/373)** Courses (Good Clinical Practices, Adverse Events, Pharmacy, Clinical Laboratory, Nursing) | **Adequate** (100%) |
| **5. Percentage of polyclinics with electronic data management** | **0%** (Paper Data collection) | **Not adequate** (<100%) | **100% (17/17)** (Training and certification of 68 users) | **Adequate** (100%) |
| **6. Percentage of polyclinics with Standard Operating Procedures (SOPs) implemented** | **0%** (SOPs designed for hospitals was used) | **Not adequate** (<100%) | **100% (17/17)** (SOPs designed for PHC centers) | **Adequate** (100%) |

**Table 2.** Process indicators in multicenter oncology clinical trials conducted in PHC in Villa Clara province. Comparison PHC vs. SHC.

| | **Secondary heath care** | **Primary health care (clinical trial program implementation)** | | |
|---|---|---|---|---|
| | **2006-2011 period (Phase III, EC IIC-RD-EC081) N=29** | **2010-2015 period (Phase IV, EC ICC RD-EC120) N=183** | **2016-2020 period (Phase IV, ECICC RD-EC-157) N=127** | **2010-2020 period N=310** |
| **Study details** | Histological confirmation of NSCLC stage III or IV, **Objective Clinical Response after oncospecific treatment, performance status≤2**, Life expectancy equal or more than 3 months | Histological confirmation of NSCLC stage III or IV, patients classified as non-tributary of any oncospecific treatment or who have received first line of chemotherapy for the advanced disease and have not any therapeutic alternatives, **performance status≤3**, Life expectancy equal or more than 3 months | Histological confirmation of NSCLC stage III or IV, patients classified as non-tributary of any oncospecific treatment or who have received first line of chemotherapy for the advanced disease and have not any therapeutic alternatives, **performance status≤3**, Life expectancy equal or more than 3 months. **Biomarker determination.** | |
| **Ethical approval** | | | | |
| **7. Time for protocol and protocol modifications ethic approval** | Protocol Ethic aproval:18 days<br>Modification 03: 7 days<br>Modification 04: 16 days | Protocol Ethic approval: 28 days*<br>Modification 01: 29 days* | Protocol Ethic aproval:22 days*<br>Modification 01: 4 days*<br>Modification 04: 12 days* | |
| **Recruitment and retention** | | | | |
| **8. Province recruitment vs. total trial recruitment** | 5.8%<br>(29/497) | 17.3%*<br>(183/1058) | 17.1%*<br>(127/741) | 17.2%*<br>(310/1799) |
| **9. Proportion of patients recruited/incidence of disease** | 2%<br>29/1214 | 27.8%*<br>183/658 | 8.6%**<br>127/1463 | 14.6%*<br>310/2121 |
| **10. Inclusion rate (patients included / month)** | 0.36<br>(29/79) | 6.5*<br>(183/28) | 2.6**<br>(127/48) | 4.0*<br>(310/76) |
| **11. Percentage of randomized participants who have withdrawn consent to continue in the study** | 10.3%<br>(3/29) | 9.2%*<br>(17/183) | 10.2%*<br>13/127) | 9.6%*<br>30/310 |
| **Protocol compliance (Adherence)** | | | | |
| **12. Percentage of protocol deviations (non-compliance with treatment scheme)** | 6.8%<br>(2/29) | 4.3%*<br>(8/183) | 7.0%*<br>(9/127) | 5.4%*<br>(17/310) |
| **Management of adverse events** | | | | |

| | | | | |
|---|---|---|---|---|
| **13. Number of grade 3-4 related adverse events per number of enrolled participants** | 6.0% (2/29) | 2.1%* (4/183) | 1.5%* (2/127). | 1.9%* 6/310 |
| **14. Number of serious related adverse events reported per number of enrolled participants** | 6.0% (2/29) | 3.8%* (7/183) | 0.7%* (1/127) | 2.5%* 8/310 |

**Legend: Indicator evaluation: *Adequate, **Not adequate.**

Other Study details are available in the web sites: http://rpcec.sld.cu/trials/RPCEC00000161-En, http://rpcec.sld.cu/trials/RPCEC00000181-En and http://rpcec.sld.cu/trials/RPCEC00000205-En