The Investigational Clinical Center: a clinical-supportive and patient-centered trial unit model.

Ten years of experience through normal and pandemic times of a large pediatric Trial Center in Italy.

Authors' list and affiliations

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Abstract

Evidence-based medicine relies on appropriately designed, conducted and reported clinical trials (CTs) to provide the best proofs of efficacy and safety for pharmacological and non-pharmacological treatments. Modern clinical research features high complexity and requires a high workload for the management of trials-related activities, often hampering physicians'participation to clinical trials. Dealing with children in clinical research adds complexity: rare diseases, parents or legal guardian reluctance to engage and recruitment difficulties are major reasons of pediatric trials failure.
However, because in paediatrics many treatments are prescribed off-label or are lacking, well-designed clinical trials are particularly needed. Clinical Trial Units (CTUs) are indeed an important asset in the implementation of clinical trials, but their support to investigators is limited to administrative and non-clinical tasks. In this paper we present the model of the Investigational Clinical Center (ICC) of the Bambino Gesù Children's Hospital in Rome. The ICC includes clinicians supporting the Principal Investigators (PIs) for clinical management of enrolled patients in compliance of Good Clinical Practice, the legal framework of Clinical Trials. Furthermore, we present ten years' experience in paediatric clinical trials and how it has been disrupted during the COVID-19 pandemic. The activity of the ICC has been evaluated according to six metrics of performance. The ICC model offers a complete support, helping investigators, patients and their families to overcome majority of barriers linked to clinical research, even in time of pandemic. We propose this organization as an innovative model for total-supportive and patient-centered clinical trial implementation.

Key words: Clinical Trial Unit, Trial implementation, Trial management, Research staff, Pediatric Clinical Research, Pediatrics**.**

Abbreviations:

AE = Adverse Event

CRF = Case Report Form

CTU = Clinical Trial Unit

GCP = Good Clinical Practice

ICC = Investigational Clinical Center

IMP = Investigational Medical Product

PI = Principal Investigator

SIV = Site Initiation Visit

Introduction:

Clinical trials (CTs), when appropriately designed, conducted and reported, provide the best evidence of efficacy and safety for pharmacological and non-pharmacological treatments, but are increasingly expensive, complex, and need highly specialized competencies [1].

Trials are particularly lacking in children: in this population evidence of safety and efficacy of drugs is scarce, and off-label prescription is a common practice, with potential issues for patients' safety [2-5]. Trials in children aim to determine appropriate dosage for different age groups [3,6,7], which feature large variability in pharmacokinetics and pharmacodynamics [8,9]. Developing and conducting pediatric trials poses also important challenges for specific regulatory and ethical aspects, including specific risk/benefit assessment, provision of parental informed consent and age-appropriate children assent [10,11].

Principal Investigators (PIs) and their close collaborators dealing with pediatric trials are often

chosen by Sponsors mainly for their specialized clinical competence and for their access to the population for which the clinical trial is designed. Their knowledge in the condition under treatment is indeed important in a clinical trial, however the main issues related to trial conduction involve non-specialized clinical activities and non-clinical tasks.

During the first months of 2020, the SARS-CoV-2 pandemic determined the rise of a great number of new difficulties in clinical trials implementation, related with the procedures to prevent the spread of the novel virus. Drug regulatory agencies including EMA, FDA and the Italian drug regulatory agency AIFA released guidelines for opening new trials and conducting ongoing trials during COVID-19 public health emergency [12-14]. Those documents gave the appropriate instructions, in circumstance of additional burdens and hurdles for the investigators to overcome.

In the last decades, a number of Clinical Trial Units (CTUs) were recently established as multidisciplinary units with the remit of supporting clinicians in the management of trials [15]. CTUs indeed represent an essential support in the development and management of clinical trials and generally include study coordinators, data managers, statisticians and personnel who help clinicians in performing administrative activities such as regulatory and start-up procedures, electronic data capture, study documentation archiving, clinical and monitoring visits planning [16,17]. CTU assistance does surely improve trials implementation, but it does not address all the barriers to clinician participation in clinical research, particularly those related to the trials clinical activities [18].

Investigators and study nurses are key figures for all clinical trials, as they perform clinical tasks required by the protocol and assess the safety and the efficacy of the investigational treatment, the permanence of a patient in a trial, the severity and causality of adverse events (AEs). These duties, together with many other barriers associated to the growing complexity of trials procedures, and the lack of time due to standard clinical obligations, hamper the participation of clinicians to clinical trials, and ultimately slow down clinical research [19,20].

In this paper we discuss the organization and structure and present the ten years' experience of the "Centro Trials" of Bambino Gesù Children's Hospital, a model of Investigational Clinical Center (ICC). In this model, personnel of ICC (physicians, research nurses, study coordinators) are fully included in the study staff delegated by PIs of the Hospital, which belong to different clinical specialties (such as cardiology, nephrology, neurology, etc.). ICC physicians take the role of sub-Investigators and take over clinical duties requested by the protocol. We also report the activity of the center during the COVID-19 pandemic, discussing the difficulties encountered in conducting clinical trials in the context of a general lockdown. Finally, we propose and discuss here an approach for the measurement and the evaluation of ICCs and CTUs performances.

Methods

We described the ICC model and reported its activity in pediatric clinical research according to six metrics of performance. To identify those metrics, we performed a literature review on Pubmed, searching for indicators of trial conduction performance. The activity of the Bambino Gesù Children's Hospital ICC was assessed in the time period from its establishing in 2010 to June 2020.

We also collected investigators' satisfaction for ICC's support by mean of a questionnaire delivered to the PIs of the trials conducted in the Hospital in collaboration with the center. The questionnaire was structured in domains which the PIs could evaluate from a minimum of 1 (absolutely not satisfied) to a maximum of 5 (very satisfied). The questionnaire is available in the supplementary material. The analysis included data of interventional, translational and observational studies supported by the ICC.

Results

Description of ICC structure and medical personnel

The ICC is characterized by the presence of physicians totally dedicated to trial-related clinical activities under delegation of the PI: collection of informed consent/assent, evaluation of inclusion/exclusion criteria, randomization, physical examination, evaluation of laboratory results, adverse events recognition and report, timely communication of serious adverse events, assessment of causality of adverse events, assessment of clinical endpoints.

Research nurses of the ICC are also totally dedicated to clinical trial procedures and provide procedural support to the trial investigators: planning and execution of protocol procedures, study drug preparation and administration, vital signs assessment, collection, processing, storage, management and shipment of biological samples, management of laboratory kits and medical equipment, and test execution and transmission. Study coordinators support the start-up process, organize visits procedures, complete case report forms (CRFs) with trial patients' data and help sponsor delegated clinical research assistants (CRA) in their monitoring visits at the IC. Furthermore, they work closely with clinical staff, providing timely information about trial's required data.

A quality assurance (QA) manager and auditor implement a Quality System, supporting development and update of Standard Operational Procedures for Trial activities in agreement with current international and national laws. Administrative personnel take care of trials budget preparation and management, and of patients travel reimbursement.

All ICC's personnel are trained in Good Clinical Practices (GCP) and take part in feasibility visits and site initiation visits (SIVs). They act also as trainers to PIs and their entourage for GCP and trial procedures, organize annual GCP courses for Hospital and external investigators and ultimately promote a Hospital-wide clinical research culture. Moreover, the ICC personnel offer their methodological services to various stakeholders (including independent researchers and drug

companies), supporting not only the conduction but also the design and development of clinical trials.

The ICC works closely with other Hospital Units, such as: Radiology, Laboratory, Intensive Care Unit, Ethical Committee and the Hospital Pharmacy, which provides pharmacists and structures dedicated to IMP management, and many of the hospital's clinical wards.

The ICC features dedicated facilities to ensure efficient conduction of clinical trials, including dedicated rooms for medical visits, drug infusions, monitoring visits, archive, and a samples' processing room with regularly monitored equipment (centrifuge and freezers) according to the requirements of Good Clinical Practices (see Supplementary Material S1).

The ICC is certified to the Italian Health Ministry for performing Phase I trials, and also accredited according to quality standards system UNI EN ISO 9001:2015 and Joint Commission International.

Performance Metrics

The literature review on Pubmed showed paucity of relevant publications regarding performance indicators of trial implementation. A few years ago, the NIH sponsored the realization of common clinical research metrics through the Clinical and Translational Science Awards (CTSA) program [21]. Recently, Withman et al. provided a standardized set of metrics for monitoring clinical sites performance involved in multicenter trials [22]. Taking inspiration from these studies, we produced a list of metrics that could fit our purpose to properly assess the performance of organizations deputed to the implementation of clinical trials. This list also includes some metrics used in the internal ISO procedures.

We divided the metrics of performance in three main distinct areas, considering:

1. Overall activity:
    a. number of new opened trials per year;
    b. number of active trials per year.

2. Recruitment and retention:
    a. ratio of final number of enrolled patients over expected as stated in the contract agreement per year;
    b. dropout ratio (% of patients that prematurely ended their study participation after enrolment for own decision or protocol deviation) on the total of randomized patients per year.
3. Protocol Compliance:
    a. percentage of randomized patients with at least one protocol violation.

The ICC of the Bambino Gesù Children's Hospital showed a positive trend in the overall activity metrics: in the period from January 2010 and December 2019 the number of opened studies amounted to 180. The number of active studies per year from 2010 and 2018 increased almost constantly, moving from 18 active studies in 2010 to 83 active studies at the end of 2019 (Figure 1). The number of new opened trials per year ranged from a minimum of 10 to a maximum of 31 (Figure 2).

The recruitment and retention metrics are of relevant importance, as the enrolment phase is particularly critical in pediatric trials. The average ratio of final number of enrolled patients over the expected per year was 74%. The dropout ratio per year in the 2010-2019 period ranged from a minimum of 0% in 2015 to a maximum of 14.3% in 2016, for a total of 31 dropouts, mostly due of perception of lack of drug efficacy or consent withdrawal. The percentage of patients with protocol violations amounted to 0%.

Performance metrics during the COVID-19 pandemic

From the 1st of January 2020 to the 30th of June 2020, which included the lockdown period due to SARS-CoV-2 spread containment in Italy (from 8th March to the 3rd June), 11 new studies managed by the ICC were started. The dropout ratio in 2020, till the end of June, amounted to 4.5%,

for a total of 1 dropout, due to lack of compliance with study procedures. The percentage of patients with protocol violations amounted to 0%.

The Principal Investigators' Satisfaction Questionnaire

The principal investigators' questionnaire was given to 43 PIs and was answered by all. On a five-point scale the overall mean value was 4.68 (SD 0.12) points. The "clinical support" domain of the PIs' questionnaire, related to the assistance in basal clinical care of the enrolled patients, achieved 4.60 (SD 0.62) points. The best evaluation was given to the safety domain, attaining to the support in pharmacovigilance activities, which accounted for 4.88 points (SD 0.80), while the lowest was "interactions with ethic committee" accounting for 4.49 points (0.32) (See Table 1).

DISCUSSION

Performing pediatric trials involves important burdens both in terms of time for non-clinical and clinical activities. It requires specific knowledge and multidisciplinary competences in terms of regulatory, ethic and scientific expertise, which may represent a barrier for clinicians busy with routine clinical duties. Indeed, clinicians are often not willing to participate in clinical trials due to many related complexities and burdens. In a survey conducted among American pediatricians, the training of the site staff in clinical research procedures resulted as one of the main barriers for participating in a trial [23]. Moreover, lack of time due to daily clinical care is also regularly reported as a significant obstacle restraining physicians from participating in clinical research [19,20].

Nonetheless, most CTUs are structured to support and control the administrative tasks of the trials (such as data entry, randomization of enrolled subjects, etc.) leaving all the clinical tasks to PIs and their close collaborators [16,17].

Indeed, in the history of clinical research, different models have been adopted for the implementation of clinical trials:

- Standard Clinical Trial Site: trials conducted in hospital wards, PI and Sub-Investigators not supported in any of the trial activities;
- Supported Clinical Trial Site: a CTU supports PI and Sub-Investigators in administrative and non-clinical activities;
- Investigational Clinical Centre: PI and Sub-Investigators are totally supported not only in administrative activities but also in clinical duties by physicians, nurses, and study coordinators fully dedicated to trials.

We present in Box 1 a scheme of the evolution of organization models of clinical research, with the pros and cons of each model.

The ICC of Bambino Gesù Children's Hospital became operative in 2010, with the aim of supporting PIs and performing both administrative and clinical activities required by the trials. The support provided is both in terms of human resources and of dedicated structures and facilities.

The ICC of the Bambino Gesù Children's Hospital is led by a core team of clinicians, who support PIs and specialist sub investigators in conducting the trials and helping in the clinical management of the trial subjects. In this model, the investigators are supported by ICC's physicians and nurses, who are confident with the clinical duties common to all trials, such as timely AEs and SAEs report with causality assessment, randomization, drug administration and compliance. With this organization, the PI-specialists (e.g. cardiologist, neurologist, endocrinologist, etc.) are relieved of the great part of the trial burden, and therefore only have to deal with the specific disease clinical course of the enrolled patients; this helps them to overcome the difficulties of participating in clinical research.

Moreover, PI and sub-investigators have more time to identify and establish a dialogue with candidate participants for the trial, allowing the enrolment of a greater number of patients.

The ICC supports studies in many different therapeutic areas (see Supplementary Material S3), but not in oncology, for which there is a dedicated trial center at the Bambino Gesù Children's Hospital.

The ICC features its own dedicated spaces, providing investigators with an efficient infrastructure to recruit, perform and manage clinical trials, far from the crowd of clinical wards and ambulatories.

However, it should be highlighted how not only clinicians benefit from the ICC support: first of all, it guarantees children a safe and reliable administration of experimental drugs in a caring and dedicated environment. ICC clinical personnel only deal with patients recruited in clinical trials, ensuring that a greater attention is paid to each one of them. Moreover, it provides a private place where parents and children can relate with clinicians and share their experience with other families or patients. This is important to make them feel comfortable, facilitating the building of trust between clinicians and families. Doctor-child and doctor-parent relationships are indeed essential in pediatric research, as the parents' willingness to enroll their children in a clinical trial depends on the benefits and risks of the trial perceived during presentation of the study and informed consent and assent acquisition [24]. One of the main problems related to pediatric clinical trials' failure is the difficulty in enrolling subjects, which often leads to issues in the trials completion [25].

The standardized metrics for analyzing the performance of the ICC may represent a user-friendly tool that can be adopted for longitudinal performance assessment and comparative assessment within other sites.

To the end of 2019, the trials followed with the support of ICC of the Bambino Gesù Children's Hospital contributed to provide evidence for the approval of 9 drugs in the pediatric population. These are now currently used for the treatment of different conditions and rare diseases, including Cystic Fibrosis, Duchenne Muscular Dystrophy, Batten disease and Spinal Muscular Atrophy (See Supplementary Material S2). The Overall Activity metrics showed a positive trend in the center performance. Anyway, we could not compare the trial metrics before and after the creation of the ICC or with other pediatric CTUs with other structures. A comparison could have better shown a

difference between the presence and absence of ICC support. The percentage of enrolled patients out of the expected by the PI, depends both on the ability of the ICC in the enrolment phase but also by the capability of the PIs in identifying possible individuals for the trial. Indeed, an ICC requires numerous resources and not every health care facility may be able to implement them.

During the COVID-19 pandemic, more difficulties were added to clinical trials conduction, as patients could not always come to attend the study visits at the site. In particular, the precautionary measures adopted were the following: we have limited the number of visits per day, allowing access to only one guardian per minor, each individual visit to ICC was scheduled at exact time in order to avoid crowd, rooms were sanitized after each visit, patients and guardians were asked to wear facial masks, safety telephone screening with body temperature assessed were performed the day before visit.

According to the regulatory agencies'recommendations, the visits at the clinical site, when possible, were replaced with phone calls and investigational drug was sent directly from the hospital pharmacy to the patient's home [13,14]. Monitoring visit were performed in remote modality, with supplemental activities of ICC study coordinators. In the case of update calls, the procedure was carried out without further authorization, while in the case of video calls that required Source Data Verification (SDV), the sponsor had to request prior authorization to the Institutional Data Protection Officer.

There was a case-by-case risk/benefit discussion between PI, ICC Investigators, and Sponsor on the opportunity to perform on-site visit or remote visits. When patients had to necessarily be visited in person, they had to be tested with rhino-pharyngeal swab for Sars-CoV-2 previously to the clinical visit. During each visit physicians, nurses and patients had to wear individual protection devices such as surgical masks.

Moreover, many clinical sites were closed or unavailable. Bambino Gesù ICC carried out some visits of patients followed in clinical sites in Lombardy, the region mostly hit by epidemics.

Despite these additional hurdles, the ICC managed to maintain its activities, as shown by performance metrics values in the first half of 2020.

As already mentioned, pediatric clinical trials are constantly increasing in number and quality, posing several challenges that stakeholders must deal with. Many specific networks have risen in recent years with the objective of addressing these challenges. In Italy, the creation of a network for multidisciplinary clinical trials in the pediatric field has been missing, more likely due to the lack of an organized management of the available resources. The ICC of the Bambino Gesù Children's Hospital is one of the founding members of INCiPiT (Italian Network for Pediatric Clinical Trials), a no-profit Consortium composed by the main Italian children's hospitals, the largest departments of pediatrics as well as national and International pediatric therapeutic networks coordinated by Italian institutions. The scope of INCiPiT is to foster high-quality research on drugs in children in Italy; INCiPiT aims to support the planning, conduction and completion of all types of clinical studies in the pediatric population, by providing expertise and coordinating logistical support to academic investigators as well as to pharmaceutical industries and contract research organizations.

As Pediatric Networks have the aim to facilitate the identification and allocation of sites suitable for a specific clinical trial, new models of support unit are required to facilitate the execution of clinical trials, also capable of acting in emergency context like COVID-19 pandemic.

CONCLUSIONS

In literature, it has been highlighted how CTUs provide an important assistance but are not exhaustive and cannot address many barriers and issues related to clinical research [18].

The metrics we propose for the assessment of a CTU's activity could represent a simple and valid method to evaluate a CTU's performance in time. The ICC of the Bambino Gesù Children's Hospital considerably increased in time its burden of activities, conducting overall more than 150

trials, following more than 400 patients of more than 15 different nationalities, and becoming an important international site in the field of pediatric research. In our opinion, the ICC represents an improved model for clinical trials management, providing complete support to both investigators and patients, and could be a sound answer to the needs of clinical research.

Declarations:

•**Ethics approval and consent to participate:** all the studies here described where approved by local Ethic Committee, and all the participants and legal guardians provided written informed consent or assent when minors.

•**Consent for publication:** all the participants and legal guardians provided written informed consent or assent when minors for using clinical data for publications.

•**Availability of data and materials:** •The datasets generated and/or analysed during the current study are not publicly available due to presence of personal and confidential data.

•**Competing interests** The authors declare that they have no competing interests

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•**Authors' contributions:** GP conceived the study. GP, SL, AS, PR participated in its design. IB, RC, GC, CF, FM collected the data and drafted the manuscript. GP, FDC, MC analyzed the data and drafted the manuscript. FR revised the paper and provide information on networks. All authors read and approved the final manuscript.

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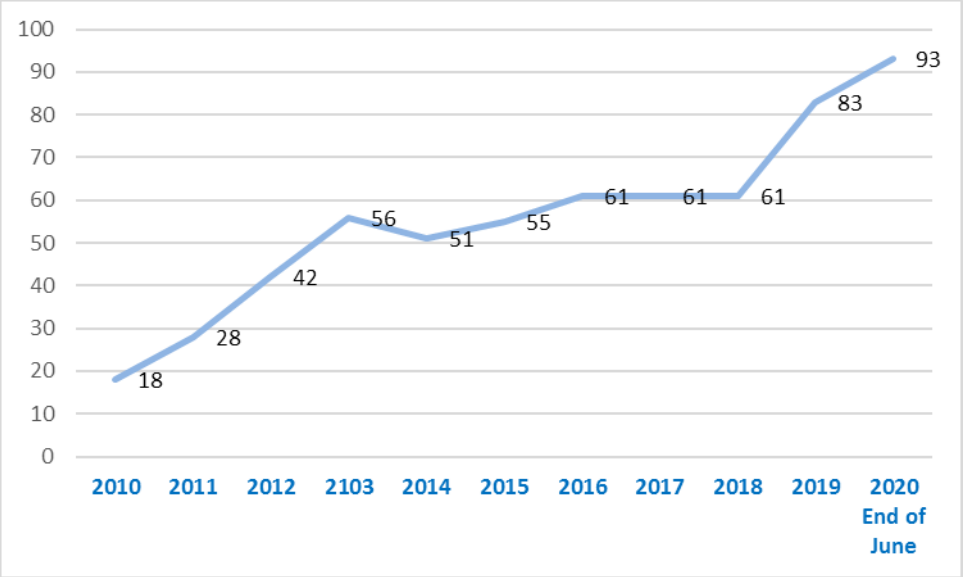


Figure 1. Number of active trials supported by the ICC per year.

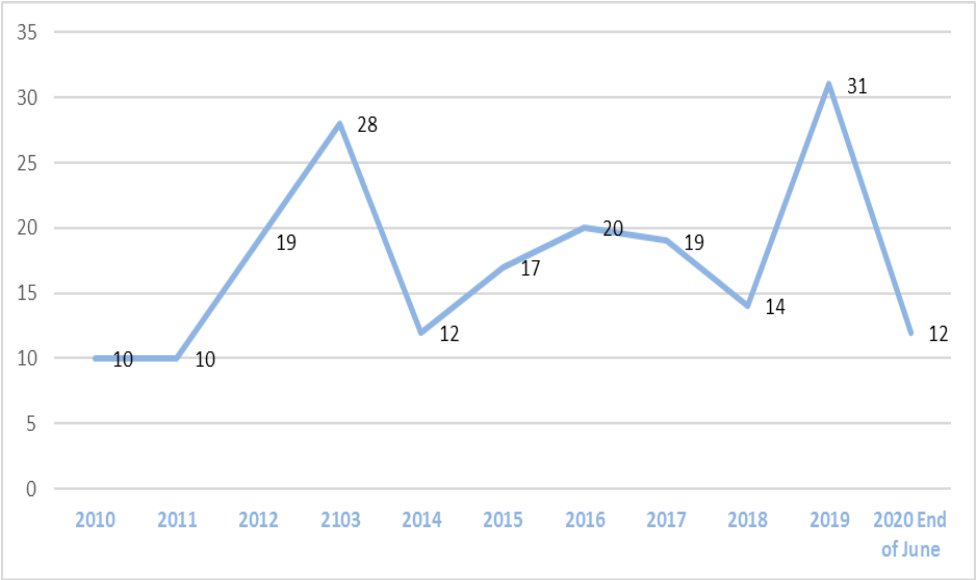


Figure 2. Number of new opened trials supported by the ICC per year.

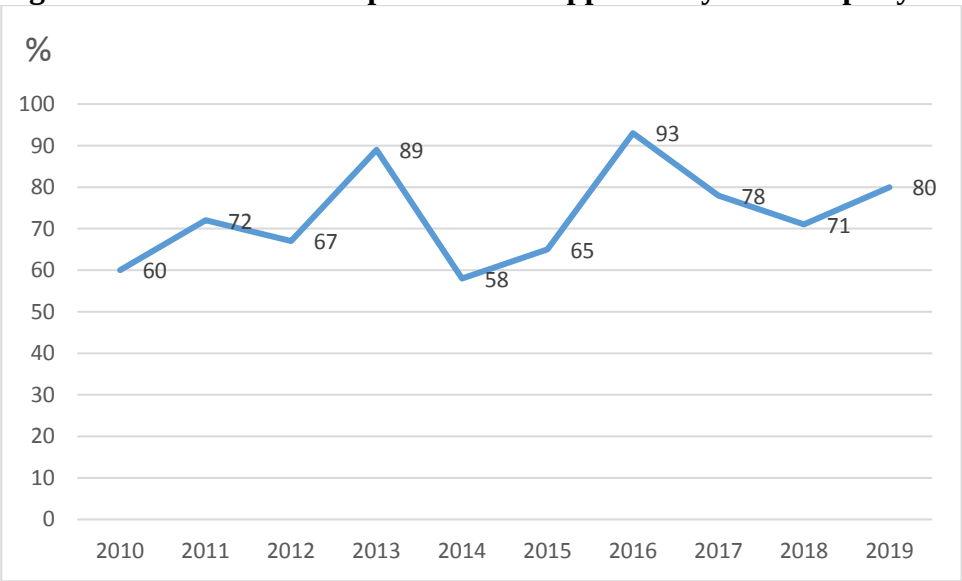
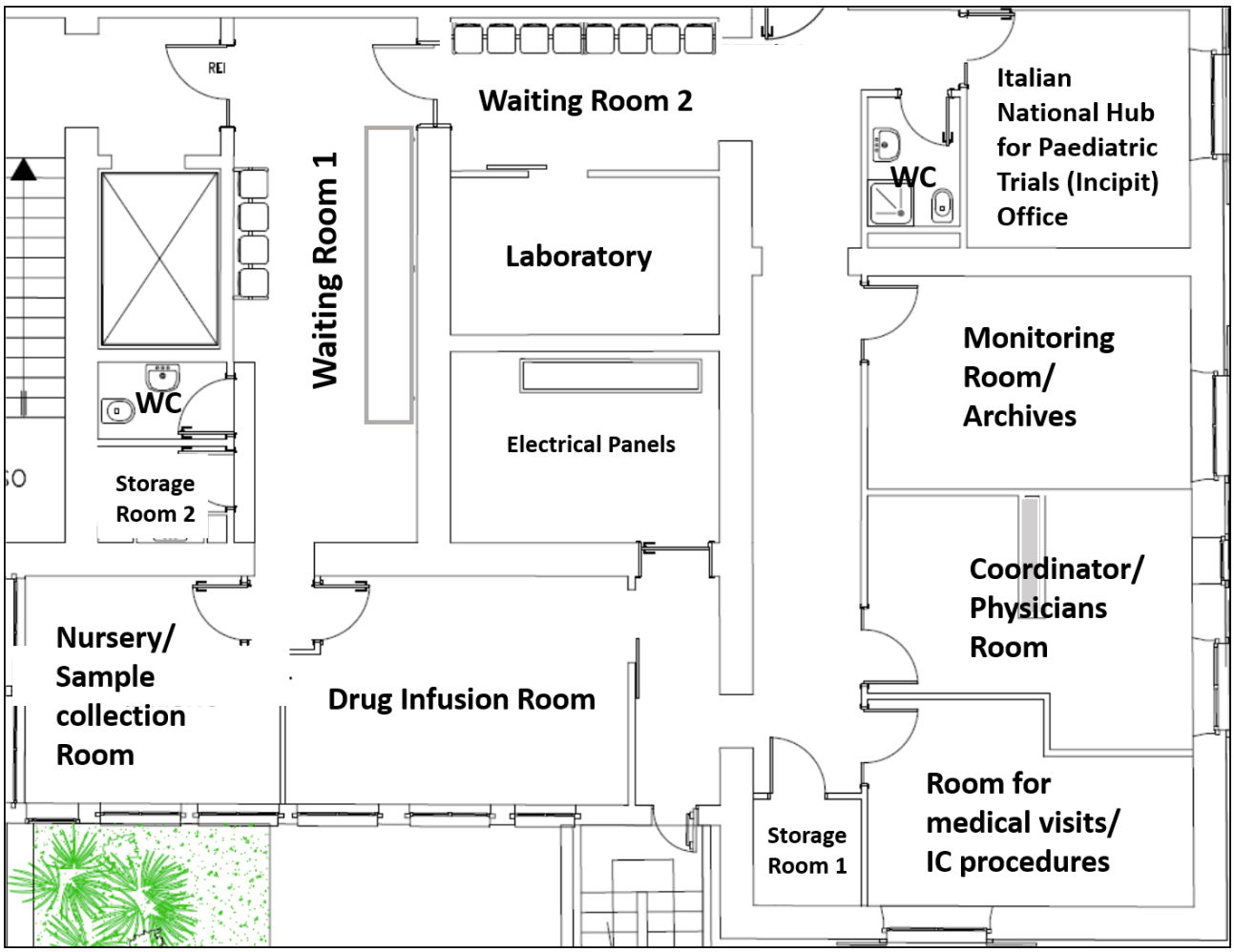


Figure 3. Ratio (%) of final number of enrolled patients over expected.

Feasibility	Enrollment Procedures	Trial Visits Planning	Clinical Support	Nurse Support	Monitoring/ interactions with Sponsors	Ethic commitee interactions	Data entry	Safety
4,60 (0,66)	**4,58 (0,85)**	**4,77 (0,48)**	**4,60 (0,62)**	**4,67 (0,57)**	**4,74 (0,49)**	**4,49 (0,80)**	**4,79 (0,47)**	**4,88 (0,32)**

Table 1. PIs questionnaire results. Mean (SD). The evaluation range goes from a minimum of 1 (the PI evaluate to have been not helped at all by the IC) to a maximum of 5 (the PI evaluates the IC support as significant)

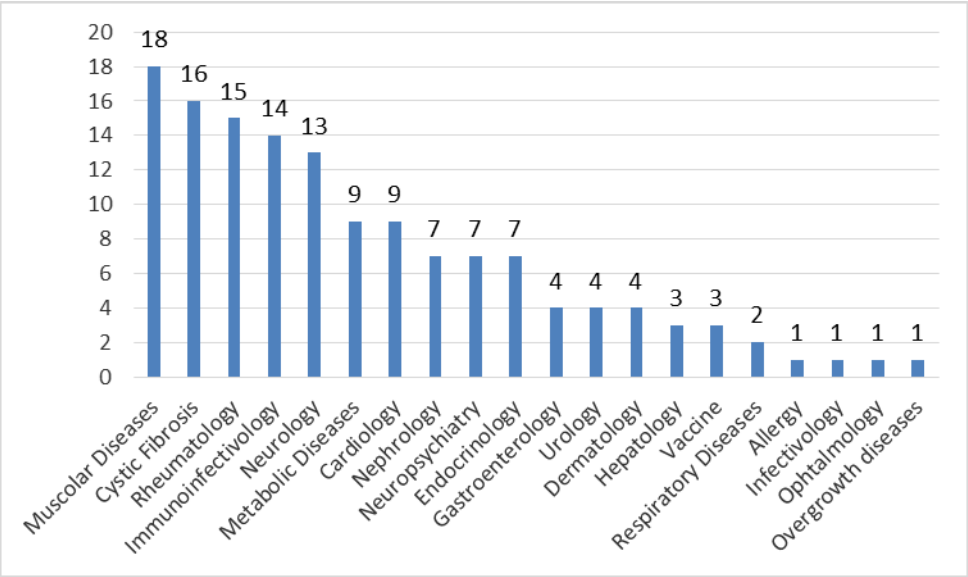
Box 1. Different models for the implementation of clinical trials.



Supplementary Material S1. Investigational Clinical Center of Bambino Gesù Children Hospital planimetry.

Drug Name	Type of Drug	Adult drug indication
Tocilizumab	Biological	Juvenile idiopathic arthritis
Kuvan	Chemical	hyperphenylalaninemia (HPA) and phenylketonuria (PKU)
Ataluren	Chemical	Duchenne muscular dystrophy
Degludec	Biological	Type I diabetes mellitus
Canakinumab	Biological	Recurrent family fevers
Cysteamine	Chemical	Cystinosis
Lumacaftor /Ivacaftor	Chemical	Cystic fibrosis
Asfotase	Biological	Pediatric-onset hypophosphatasia
Nusinersen	Biological	Spinal Muscular Atrophy

Supplementary Material S2. List of the drugs Bambino Gesù Children's Hospital ICC contributed to approve in the pediatric population.



Supplementary Material S3. Number of trials per disease supported by the Bambino Gesù Children's Hospital Investigational Clinical Center.