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Clinical Study Protocol Quality Evaluation Using Adapted SPIRIT: Ospedale Maggiore di Novara.

Mentor: **Dr. Alberto Lontano**

University Supervisor: **Prof. Abdurraouf Mokhtar Saleh Mahmoud**

Firmato digitalmente da Abdurraouf Mokhtar Saleh Mahmoud
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Candidate: **Joudy Moukhtar**

Matricular Number: **20058814**

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ABSTRACT

BACKGROUND

Clear and well-structured protocols are essential for transparent and consistent clinical research. However, protocols can vary in structure and completeness, affecting study conduct. While SPIRIT provides guidance for interventional trials, its use in observational studies and in addressing some operational aspects is less clear. In this thesis, SPIRIT criteria were applied to both interventional and observational protocols, together with additional operational and governance criteria, to better evaluate how protocols are documented across study designs.

OBJECTIVE

This study aimed to apply an adapted SPIRIT-based framework to assess and improve the quality and completeness of clinical study protocols at the Clinical Trials Center of Ospedale Maggiore di Novara, including both interventional and observational designs.

METHODOLOGY

A retrospective institutional review evaluated all clinical study protocols developed at the Clinical Trials Center of the AOU “Maggiore della Carità” of Novara between 2021 and 2023. An adapted SPIRIT 2013-based checklist was applied to interventional and non-experimental studies. Items were scored as present or absent across 6 domains to calculate completeness percentages. Domain scores were compared by study year and design, and correlations with principal investigator experience and publication record were explored. Statistical analyses used appropriate parametric or non-parametric tests, with significance set at $\alpha \leq 0.05$.

RESULTS

Most protocols were observational studies without drugs. Overall completeness was moderate (SPIRIT total: 60.53%). Highest scores were found for Introduction (75%) and Data collection and analysis (70.13%), while Administrative information (55.70%) and Ethics and dissemination (48.52%) showed the lowest completeness. Core methodological elements were reported in over 90% of protocols, whereas governance and transparency items were rarely documented. Medical device studies achieved the highest completeness, and a modest improvement from 2022 to 2023 was observed in data management and ethics-related domains.

CONCLUSIONS

The adapted framework highlighted important gaps in protocol documentation, particularly in governance and monitoring. Its application across different study designs shows its potential to improve transparency, support ethics and regulatory review, and strengthen the overall quality of clinical research.

1. INTRODUCTION

1.1 Evolution of Clinical Research Standards

Clinical research is necessary to translate the scientific discoveries into clinical practice, the accuracy of any clinical study depends on the quality, structure, and clarity of its protocol. The need for standardized tools has increased to ensure the methodological rigor of clinical trials, while these trials are becoming more complicated in their design, regulation, and ethical considerations. In this context, it is crucial to have a clear understanding of the historical background of clinical research in terms of methodological, ethical, and regulatory considerations to understand the emergence of tools in the design and evaluation of various kinds of clinical studies.

The use of safer, more effective, and newer treatments has been made possible by the drug development process. Any pharmaceutical product must pass several strictly regulated testing stages before it can be made accessible to the public. These stages begin with preclinical research in animals and extend through human trials. The most critical phases in this process are the clinical trials, as they are the basis for the evaluation of the efficacy, safety, and feasibility of new medications and diagnostic tools. Clinical trials have translated the results of animal studies and laboratory research into safe and effective medical practice [1].

An important turning point in medical research was in 1747 when the Scottish naval surgeon James Lind conducted the first recorded clinical trial to evaluate treatments for scurvy in sailors aboard the HMS Salisbury.

Over time, clinical research evolved from simple observational methods to complex research methodologies guided by scientific principles. This evolution became particularly evident in the mid-20th century, when the growing complexity of drugs and medical devices highlighted the importance of a more refined evaluation approach. The introduction of randomization by Austin Bradford Hill in the 1940s, followed by the development of double-blind study designs in the 1950s, represented major milestones in the history of clinical trials and greatly improved the reliability and validity of clinical research findings [2].

Alongside the evolution of trial methodologies, the ethical foundations of clinical research have also developed in response to major historical events. An important landmark in the development of research ethics was the creation of the Nuremberg Code, which has served as a fundamental reference for ethical clinical research since its adoption in the period following the Second World War [3]. It was developed in response to the inhumane medical experiments carried out by Nazi physicians and investigators, the Code brought attention to the protection of participants and to the ethical responsibilities of researchers. Within this context, the Nuremberg Code introduced key ethical principles, as informed consent and to harm minimization, which became central elements of modern clinical research practice. These principles then developed the international ethical frameworks and contributed to the standardization of clinical trial conduct and documentation. [3]

Building on these foundations, the Declaration of Helsinki, first adopted in 1964, further expanded and refined ethical guidelines for medical research involving human subjects. [2] Within this ethical and methodological evolution, the standard of clinical research was further enhanced by the introduction of Randomized Controlled Trials (RCTs), along with adaptive trial designs and cluster randomized trials. In order to guarantee high standards and ethics,

modern trials are regulated by standardized protocols like CONSORT (1996) and Good Clinical Practice (GCP) guidelines.

Clinical trials are now more patient-centred and concentrate on results that have an impact on patients' quality of life. This change reflects the increased focus on ethics and the applicability of research findings [2].

Based on this, clinical trials can be also distinguished according to their design, objectives, and data collection methods into two general categories: observational and interventional studies [8].

Observational studies are one of the most frequently carried out forms of clinical research, it aims to identify risk factors, detect the presence or absence of specific conditions, and determine their prevalence or incidence in a population.

Clinical trials are categorized as either therapeutic or non-therapeutic based on the nature and intended purpose of the intervention, although such studies may contribute to future improvements in treatment and clinical practice [4].

Because of the diversity of clinical trial designs and the potential risks related to research involving human subjects, the establishment of a comprehensive regulatory framework became essential to ensure consistent standards, participant protection, and scientific quality across countries.

1.2 European Regulation for Clinical Trials

The European Union took its first significant step to harmonize clinical trial laws in 2001 by introducing the European Clinical Trials Directive (2001/20/EC), which established Good Clinical Practice (GCP) as a legal standard and aimed to improve trial participant safety, ethical oversight, and scientific quality across Member States [5].

This directive's main purpose was to create a uniform framework for conducting clinical trials involving pharmaceuticals and human subjects which was a huge step forward in the rules for clinical trials. This included studies involving human subjects aimed at evaluating the clinical, pharmacological, and pharmacodynamic effects of investigational medicinal products. Such studies also examined adverse effects and pharmacokinetic characteristics, as drug absorption, distribution, metabolism, and excretion, with the objective of assessing safety and efficacy [6].

Unfortunately, Directive 2001/20/EC had a number of critical flaws, including the requirement to submit separate applications for trials conducted across several countries, unnecessary and heavy administrative procedures, and different implementation across EU Member States. In addition, dealing with conflicting decisions, especially those made by ethics committees, and prolonged approval timelines [7].

As a result, Regulation (EU) No. 536/2014 was adopted by the European Parliament and Council, which is known today as the European Clinical Trials Regulation (ECTR). The objective of this regulation is to have more efficient and harmonized administrative processes for multicenter clinical trials among EU member states which will speed up the application process. Unlike previous directives, the ECTR applies to every member state, and introduced

centralized processes through the Clinical Trials Information System (CTIS), aiming to reduce bureaucracy, improve transparency, and facilitate multicenter research [5].

Beyond these regulatory rules, the heart of any clinical trial lies in its design. This begins with a fundamental choice: conducting an observational study or an interventional one.

1.3 Observational and Interventional Studies

Choosing an appropriate study design is only one element of effective research. Reviewing relevant published standards during the planning phase can significantly improve the execution and interpretation of study findings.

Primary research studies are divided into two categories: Observational and Interventional.

Observational studies, also known as epidemiological studies, involve the investigator observing and evaluating natural relationships between variables and outcomes without taking any active action on study participants.

In contrast, interventional or experimental studies require the researcher to introduce an intervention or modify conditions as part of the study design [8].

Time also plays an important role in data collection, which distinguishes these studies according to the temporal direction of data collection into:

Retrospective studies use data that already exists or participant memories of past events, either from previously created records or by asking participants to recall their experiences.

Prospective studies track participants over time and gather data during the study period [8].

Understanding the differences between observational and interventional studies is essential for planning and reporting clinical trials. This knowledge demonstrates the value of tools like SPIRIT, which help translate information into practical guidance for building and developing reliable protocols.

1.4 SPIRIT Instruments

A research protocol is an essential component of any clinical study, and its definition and level of detail may vary among different investigators, sponsors, and research institutions. In general, the protocol should offer a precise and organized explanation of the scientific background, rationale, objectives, study design, methodology, ethical considerations, and administrative aspects of a study, enabling transparent understanding and reproducibility of the planned research [10].

Despite the critical role played by clinical trial protocols in guiding all aspects and phases of the clinical trial, from participant recruitment to results dissemination, studies have shown that the quality of clinical trial protocols is often insufficient. Incomplete protocols may limit transparency for stakeholders responsible for participant safety, study design, data integrity, and oversight, potentially affecting trial conduct, reporting, and external review. Clear documentation of trial elements, such as study timelines, interventions, outcome measures, and statistical methods, facilitates proper trial implementation and critical analysis [11].

High-quality clinical trial protocols are not only essential documents but also fundamental components in ensuring proper trial conduct across different settings and reducing uncertainty for investigators, sponsors, ethics committees, regulatory agencies, and other stakeholders involved in overseeing clinical research [11].

Moreover, evidence from pharmaceutical industry trials indicates that a large part of protocol amendments could have been avoided through greater attention to many methodological and organizational aspects during the protocol development phase [11].

In response to these documented limitations, an international group of stakeholders launched the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials). This initiative resulted in the publication of the SPIRIT 2013 Statement, aiming to promote a comprehensive and standardized approach to protocol development, ensuring that essential methodological and ethical elements are clearly and consistently documented [10].

The SPIRIT Statement provides evidence-based recommendations outlining the minimum information required to describe a randomized controlled trial (RCT) protocol. The checklist consists of 33 items and focuses on protocol content rather than format, offering guidance to support the development of high-quality and comprehensive trial protocols [10].

Section/item	Item N	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable
DMC= data monitoring committee; IRB = institutional review board; REC = research ethics committee; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.		

Figure 1. SPIRIT 2013 Checklist: Recommended Items to Address in a Clinical Trial Protocol and Related Documents [10].

The checklist has undergone several revisions and defines the protocol as a comprehensive document that details the background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans, trial administration, replication of key aspects of trial methods, and evaluation of the trial's scientific and ethical reliability from ethics approval to results dissemination [10].

Although SPIRIT was originally developed for interventional randomized trials, several of its core items address fundamental methodological components that are also applicable to other types of clinical research, including observational study protocols. These include the clear definition of objectives, outcomes, eligibility criteria, data collection procedures, data management, statistical analysis plans, and ethical considerations, which represent essential elements of any well-designed research protocol regardless of study design [10]. Following SPIRIT encourages investigators to systematically consider critical methodological and ethical issues during the planning phase, which may enhance trial validity and overall study success. Improved completeness of protocols may also increase the efficiency of protocol review by minimizing unnecessary questions to investigators about missing or unclear information, facilitate trial registration and evaluation, and highlight areas where protocols systematically fail [10].

In this sense, the protocol functions as a structured operational framework that translates a large range of methodological options into a clear course of action, guiding trial conduct across different settings and actors [12].

To further support correct interpretation and application of the checklist, the SPIRIT 2013 Explanation and Elaboration paper provides detailed guidance for each checklist item, including the underlying rationale, supporting evidence, and illustrative examples drawn from real trial protocols [11].

Despite these advantages, the use of standardized protocol frameworks requires careful and flexible application to avoid overly rigid or context-insensitive implementation [12]. It is important to note that the primary intent of SPIRIT is to promote transparency and a comprehensive description of planned trial procedures. Thus, the checklist is not intended to serve as a direct measure of trial quality, because even a methodologically weak study may fully address all checklist items [10].

SPIRIT was selected as the reference framework for this thesis because it is specifically designed to guide the development and structure of clinical trial protocols at an early stage of the research process.

By defining a standardized set of essential protocol items, SPIRIT enables systematic identification of missing or unclear elements before trial initiation [10]. Because of its international acceptance and alignment with regulatory and ethical review processes, this work extends the use of SPIRIT items to both observational and interventional studies, where there is currently no widely accepted protocol planning standard, and puts them into a structured institutional evaluation framework.

Besides SPIRIT, other complementary instruments have been developed to ensure consistent evaluation of protocol quality and overall research performance.

1.5 Instruments for Evaluating Protocol Quality and Clinical Research

Quality involves many different components, including clinical relevance, trial design, conduct, and analysis, as well as the quality of reporting [13].

Metrics and instruments can guide clinical researchers in assessing their research projects early, before making important investments. Additionally, they provide structured criteria for reviewers to evaluate grant proposals and research manuscripts. The development of these metrics typically involves several stages including literature review, instrument design, internal and external validation, and continuous revision in response to feedback [14].

In addition, a high-quality clinical trial protocol enables faster and more efficient implementation of complex study designs, which decreases the possibility of preventable protocol deviations and makes the protocol easier for less experienced clinical research staff to follow. However, currently, there is no universally accepted scoring system to evaluate clinical trial protocol documents [15].

The CONSORT (Consolidated Standards of Reporting Trials) statement is a globally recognized guideline designed to improve the reporting of randomized controlled trials. CONSORT guidance was updated based on new methodological evidence and years of experience. It provides a 25-item checklist and a flow diagram to guide the reporting of all randomized controlled trials, focusing primarily on individually randomized, two-group, parallel designs [16].

Beyond that, CONSORT has provided standards for reporting randomized trials to ensure accuracy, and reproducibility of published research. Thus, its evidence-based approach has

encouraged the development of additional reporting guidelines for observational research, diagnostic studies, meta-analyses, and systematic reviews [16].

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	

Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

CONSORT = Consolidated Standards of Reporting Trials.

Figure 2. CONSORT 2010 checklist of information to include when reporting a randomised trial [16].

Additionally, another benefit of the SPIRIT checklist is that it matches the CONSORT (Consolidated Standards of Reporting Trials) guidelines, when items related to both checklists are written and structured consistently, this link allows an easier transition from a SPIRIT-based protocol to a final report based on CONSORT.

Therefore, Pragmatic Randomized Controlled Trials in Health Care, the Clinical Data Interchange Standards Consortium Protocol Representation Group, trial registries, and other leaders of related initiatives have all worked with the SPIRIT Group on protocol standards. The aim of these partnerships is to promote international consistency in high-quality protocol content [10].

In fact, the SPIRIT and CONSORT extensions, known as InsPECT (Instrument for Reporting Planned Endpoints in Clinical Trials), are being developed according to the recommended methods for reporting guideline development by members of the Enhancing Quality and Transparency of Health Research (EQUATOR) Network. These extensions aim to enhance consistency and completeness of outcome reporting both in clinical trial protocols and reports [17].

Moving to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, which was developed as a set of recommendations to enhance the quality, transparency, and completeness of reporting in observational studies, including cohort, case-control, and cross-sectional designs. The guideline provides a checklist of 22

items aims to improve the clarity of methodological and analytical reporting in published observational research. However, STROBE was not designed to guide the prospective development or structural assessment of study protocols, as its primary focus lies on reporting practices after study completion rather than on protocol content during the planning phase [18].

The development of instruments for evaluating protocol quality has relied on structured methodological approaches, one of the most widely used methods is the Delphi process, which is a systematic, continuous communication technique designed to convert collective expert opinions into a statistically generated decision for complex problem-solving. It is very valuable in healthcare research, particularly in situations in which data may be limited, difficult to obtain, or inconsistent. Four main elements define the methodology: the anonymity of panel members, multiple repeated survey rounds, controlled feedback, and the statistical stability of the group response [19].

The process successfully reduces inherent biases like groupthink or the dominance of particular people that are frequently present in direct meetings by using anonymous feedback. In the end, by synthesizing collective intelligence, this methodical approach enables the creation of reliable practice guidelines and research priorities [19].

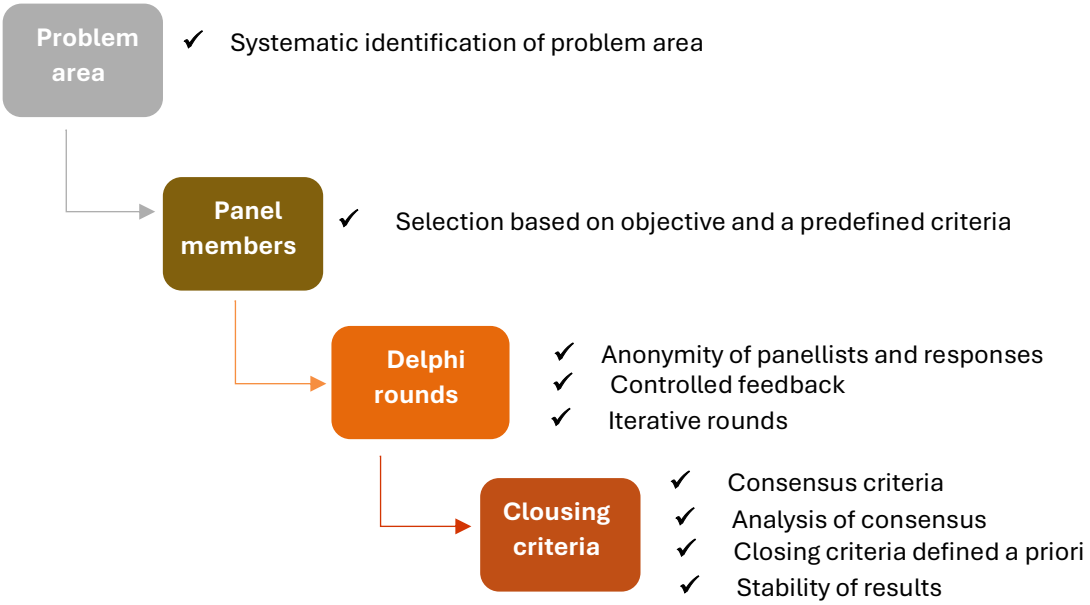

Figure 3. Stepwise quality assessment of Delphi studies [19].

Within this methodological framework, specific instruments have been developed to assess the quality of clinical trial protocols. One such instrument is the Protocol Quality Rating Tool (PQRT), which was designed specifically to evaluate the quality of clinical trial protocol documents. The PQRT was developed and tested using cognitive interviews and a modified Delphi process to ensure its feasibility and reliability.

The (PQRT) can identify whether a protocol meets the criteria of a high-quality document, as well as outline knowledge gaps and assess how training programs have affected protocol quality at the institutional or investigator level [15].

Score	Quality rating	Quality category	Criteria used to evaluate quality of section 6: endpoints
1	Exceptional	High quality	• Includes all the required elements for endpoints: delineation of primary, secondary, and exploratory endpoints; definition of what, how, and when each endpoint will be measured, and the analysis metric • Includes stated objectives or aims that correspond to the respective endpoints • The primary endpoint aligns with the main purpose of the study or is reflected in a sample size estimate/power analysis
2	Outstanding		
3	Excellent		
4	Very good	Medium quality	• Endpoints are listed, and each endpoint is defined • Endpoints are appropriately prioritized as primary, secondary, or exploratory
5	Good		
6	Satisfactory	Low quality	• Endpoints are ill-defined or vague • Endpoint description is missing at least one of the following details: what, when and how each endpoint is being measured, and analysis metric • Endpoints are not appropriately prioritized as primary, secondary, or exploratory
7	Fair		
8	Marginal		
9	Poor		
M	Missing or unable to judge		• Reviewer is unable to find element, or the information is so convoluted that the reviewer cannot assess quality

Note: Example of the rubric for assigning a score to the protocol section on Endpoints (Outcomes). Reviewers are instructed to compare the comprehensiveness, clarity, consistency, and organization of each section of the protocol document against the criteria used to assess quality for that section, and to assign a score for that section.

Figure 4. Protocol quality rating tool—scoring rubric [15].

Turning to the Jadad scale, also referred to as the Oxford Quality Scoring System, it is one of the most popular instruments for assessing the methodological quality of controlled trials. Its evaluation focuses on three main elements: randomization, masking, and patient accountability, including withdrawals. Scores range from 0 to 5, with higher scores indicating better methodological quality. Because it is simple and clear, the Jadad scale has become one of the most widely used tools for trial evaluation [20].

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/-1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/-1

Figure 5. Jadad Score Calculation [20].

And another widely used instrument, the Cochrane Risk of Bias criteria, similarly evaluate trial quality and share several items with the Jadad scale but differ by including allocation concealment and baseline data analysis. Both tools face criticism for possible limitations in fully capturing trial quality [20].

	Operationalization of Criteria
A	A random (unpredictable) assignment sequence. Examples of adequate methods are computer generated random number table and use of sealed opaque envelopes. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.
B	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.
C	In order to receive a "yes," groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurologic complaints, and value of main outcome measure(s).
D	The reviewer determines if enough information about the blinding is given in order to score a "yes."
E	The reviewer determines if enough information about the blinding is given in order to score a "yes."
F	The reviewer determines if enough information about the blinding is given in order to score a "yes."
G	Cointerventions should either be avoided in the trial design or similar between the index and control groups.
H	The reviewer determines if the compliance to the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s).
I	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored. (N.B. these percentages are arbitrary, not supported by literature).
J	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.
K	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.

Figure 6. Operationalization of the Cochrane Back Review Group Criteria List [20].

Each of these tools is based on the ethical and scientific principles of the Good Clinical Practice guidelines, which offer a structured framework for evaluating the scientific quality of research protocols while protecting the safety and rights of participants. GCP specifically states that clinical trials must be evidence-based and described in a clear and detailed protocol, which represents the primary document assessed by Ethics Committees and regulatory authorities [21].

(GCP) serves as an international ethical and scientific quality standard for the design, conduct, and reporting of research involving human participants, ensuring global acceptance of clinical data while emphasizing the need for a detailed framework that defines the specific responsibilities of all engaged parties [22].

Healthcare leaders are now able to make decisions based on evidence because of these instruments. When combined, they provide a complete structure that not only evaluates the quality, transparency, and ethical standards of clinical research but also increases the validity of trial results. Despite the widespread adoption of international guidelines, clinical research centres still struggle to maintain consistent standards in protocol development. Therefore, adapting an established protocol checklist such as SPIRIT to both interventional and observational study protocols represent a methodologically justified approach that aims to enhance protocol completeness and standardization. This adaptation also allows the specific methodological characteristics of observational research to be better captured, enabling a more precise and context-appropriate assessment of observational study protocols.

Given these considerations, this thesis aims to design and implement a SPIRIT-based dataset to assess the quality and completeness of clinical study protocols at the Clinical Trials Center of Ospedale Maggiore di Novara.

2. Objective of the Thesis

The purpose of this thesis is to develop a more uniform and complete approach for the review of clinical study protocols at the Clinical Trial Center (CTC) of Ospedale Maggiore di Novara.

Based on the SPIRIT guidelines as the main reference document, the study adapts and extends this approach beyond its original focus on interventional trials to also include observational study designs. In this regard, this work seeks to enhance clarity, completeness, and methodological quality of protocols developed within the center while reducing variability in protocol structure across different research teams.

Moreover, the proposed approach may support more efficient ethical and administrative review processes, facilitate alignment with European regulatory requirements, and provide structured guidance for less experienced investigators.

Additionally, international criteria were integrated, and a structured evaluation dataset was developed in order to support protocol assessment, facilitate monitoring activities, and promote the consistency and reliability of clinical research conducted at the center.

3. Materials and Methods

3.1 Study Design and Protocol Selection

To evaluate the quality of spontaneous research conducted at the AOU “Maggiore della Carità” of Novara, an assessment was carried out of all research protocols managed by the CTC of the AOU in the years 2021-2023 for which the AOU was the promoting center. A total of 126 protocols were identified in the CTC archive for the study period. After applying eligibility criteria and excluding protocols with insufficient information for SPIRIT-based evaluation, 80 protocols were included in the final analysis.

The years 2021-2023 were selected because they were the years for which all research protocols were available in the CTC archive when the work began in 2024.
It was decided to focus attention on non-experimental studies, as they represented by far the predominant part of the spontaneous research activity of the AOU. In 2024, although there were checklists and guidelines for evaluating the quality of published studies, systems for evaluating the quality of study protocols for observational research, medical device studies, or studies on biological samples were not yet available. Therefore, it was decided to attempt to use the SPIRIT 2013 guidelines, a tool for evaluating trial protocols, by applying them to observational studies with and without drugs, medical device studies, studies with biological samples, registries, and interventional studies conducted at the AOU.

3.2 Adaptation of SPIRIT 2013 Guidelines

Starting from the SPIRIT 2013 guidelines, some fields related exclusively to aspects typical of clinical trials and not applicable to the types of studies analyzed in this thesis were removed (in particular the Data Monitoring domain, related to the monitoring committee or auditing). Below are the included domains with the items that contributed to the development of the checklist:

Administrative information	
Title	Descriptive title identifying the study design, population, interventions, and, if applicable, study acronym
Study registration	Study identifier and registry name. If not yet registered, name of intended registry
Protocol version	Date and version identifier
Funding	Sources and types of financial, material, and other support
Roles and responsibilities	Names, affiliations, and roles of protocol contributors
	Name and contact information for the study promoters
	Role of study promoters and/or funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	Composition, roles, and responsibilities of the coordinating centre, data management team, and other individuals or groups overseeing the study
Introduction	
Background and rationale	Description of research question and justification for undertaking the study, including summary of relevant studies (published and unpublished)
	Explanation for choice of comparators
Objectives	Specific objectives or hypotheses

Study design	Description of study design including type of study (eg, study with medical device, study with biological samples, observational with drug study, observational without drugs study)
Methods: Participants, interventions, and outcomes	
Study setting	Description of study settings (eg, community clinic, academic hospital). Reference to where list of study sites can be obtained
Eligibility criteria	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (if the study is observational, the protocol should specify it is led according to clinical practice)
	Strategies to improve adherence to intervention protocols.
	Relevant concomitant care and interventions that are permitted or prohibited during the study
Outcomes	Primary, secondary, and other outcomes, including the specific measurement variable.
Participant timeline	Time schedule of enrolment, interventions, assessments, and visits for participants. A schematic diagram is highly recommended
Sample size	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Data collection, management, and analysis	
Data collection methods	Plans for assessment and collection of outcome, baseline, and other study data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	Definition of analysis population relating to protocol non-adherence, and any statistical methods to handle missing data
Ethics and dissemination	
Research ethics approval	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties, study participants, study registries, journals, regulators)
Consent or assent	Who will obtain informed consent or assent from potential study participants or authorised surrogates, and how
Confidentiality	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the study
Declaration of interests	Financial and other competing interests for principal investigators for the overall study and each study site
Access to data	Statement of who will have access to the final study dataset
Dissemination policy	Plans for investigators to communicate study results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	Authorship eligibility guidelines and any intended use of professional writers

	Plans, if any, for granting public access to the full protocol, participant level dataset, and statistical code
Appendices	
Informed consent materials	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current study and for future use in ancillary studies, if applicable

3.3 Scoring System and Additional Data Collection

For each of the items included in the six above-mentioned domains, a score of 1 was assigned if it was found in the research protocol and 0 if it was not found. An overall score was then calculated, in absolute form and as a relative percentage, for each of the domains considered and for the entire checklist.

Information was also collected on the AOU department that designed the study, on the number of publications of the Principal Investigator, and on the number of years of research activity of the Principal Investigator (calculated as the number of years elapsed since his or her first publication).

3.4 Statistical Analysis

For all variables, measures of central tendency and dispersion were calculated. Variables were tested for normality using the Shapiro-Wilk test and for homoscedasticity using Bartlett's test.

For variables with a normal distribution of sample means, the mean was used as the measure of central tendency and the standard deviation as the measure of dispersion. For those with a non-normal distribution, the median was used as the measure of central tendency and the interquartile range as the measure of dispersion.

Domain scores with normal distribution were compared according to year and study design using the ANOVA test. Bonferroni tests were used for post-hoc evaluations. In addition, for domain scores with normal distribution, the correlation with the number of years of experience of the PI and with the number of publications of the PI was assessed by calculating the Pearson linear correlation coefficient.

Domain scores with non-normal distribution were compared according to year and study design using the Kruskal–Wallis test with Bonferroni correction, given the reduced number of subjects in the comparison groups. For domain scores with non-normal distribution, their correlation with the number of years of experience of the PI and with the number of publications of the PI was assessed by calculating the Spearman linear correlation coefficient. In hypothesis testing, statistical significance was set at alpha ≤ 0.05. Statistical analyses were performed using STATA19.

4. RESULTS

4.1 Characteristics of the Included Studies

The studies of the AOU analyzed were mostly observational without drugs (37.50%), followed by interventional studies (18.75%) and studies with biological samples (15%), while the departments promoting the studies that were most represented were Cardiology (16.05%) and Clinical Biochemistry (7.41%) (see Table 1).

Table 1. Description of the sample analysed

VARIABLE		ABSOLUTE AND PERCENTAGE FREQUENCY
STUDY DESIGN	Interventional	15 (18.75%)
	Observational with drug	10 (12.50%)
	Observational without drug	30 (37.50%)
	Registry	7 (8.75%)
	Study with biological samples	12 (15.00%)
	Study with medical device	6 (7.50%)
DEPARTMENT	Anesthesiology and Intensive Care	5 (6.17%)
	Cardiology	13 (16.05%)
	Clinical Biochemistry	6 (7.41%)
	Dermatology	4 (4.94%)
	Emergency Medicine	3 (3.70%)
	Endocrinology	3 (3.70%)
	Gynecology and Obstetrics	4 (4.94%)
	Healthcare Professions	5 (6.17%)

	Haematology	2 (2.47%)
	Hospital Pharmacy	1 (1.23%)
	Infectious Diseases	1 (1.23%)
	Internal Medicine	5 (6.17%)
	Maxillofacial Surgery	2 (2.47%)
	Nephrology	2 (2.47%)
	Neurology	5 (6.17%)
	Nuclear Medicine	1 (1.23%)
	Oncology	2 (2.47%)
	Ophthalmology	2 (2.47%)
	Pediatrics	2 (2.47%)
	Physical Therapy	4 (4.94%)
	Psychiatry	2 (2.47%)
	Radio diagnostics	3 (3.70%)
	Rheumatology	3 (3.70%)
	Thoracic Surgery	1 (1.23%)
STUDY YEAR	2021	4 (5.97%)
	2022	20 (29.85%)
	2023	43 (64.18%)
		Median (IQR)
YEARS OF EXPERIENCE OF THE PI		21 (17-23)
N° OF PUBLICATIONS OF THE PI		105 (43-167)

Most studies were initiated in the years 2022 and 2023, and the median number of years of research experience of the PI was 21, while the median number of publications of the PI was 105.

4.2 Adherence to SPIRIT 2013 Checklist

Table 2 reports the absolute and percentage frequency with which the individual items of the SPIRIT 2013 domains were identified out of the total studies analyzed, while Table 3 presents the mean or median score (as applicable) expressed as a percentage for each SPIRIT 2013 domain. The highest scores were observed for the domains “Methods: Data collection, management, and analysis” (70.13%) and “Introduction” (75%), while the lowest scores were recorded for the domains “Administrative information” (55.70%) and “Appendices” (50%).

Table 2. Application of SPIRIT 2013 to AOU studies: for each item the corresponding score is reported.

Item	Yes (absolute and percentage frequency)
Administrative information	
Title	81 (100%)
Study registration	79 (97.53%)
Protocol version	63 (77.78%)
Funding	35 (43.21%)
Roles and responsibilities – name and affiliations	71 (87.65%)
Roles and responsibilities – name of PI	56 (69.14%)
Roles and responsibilities – study sponsors and funders (if any)	8 (9.88%)
Roles and responsibilities – key roles and responsibilities	22 (27.16%)
Introduction	
Background and rationale – research question	80 (98.77%)
Background and rationale – choice comparators	17 (20.99)
Objectives	80 (98.77%)

Study design	77 (95.06%)
Methods: Participants, interventions, and outcomes	
Study setting	79 (97.53%)
Eligibility criteria	74 (91.36%)
Interventions – interventions for each group	66 (81.48%)
Interventions – criteria for discontinuation	6 (7.41%)
Interventions – strategies to improve adherence	6 (7.41%)
Interventions – concomitant care	3 (3.70%)
Outcomes	80 (98.77%)
Participant timeline	56 (69.14%)
Sample size	71 (87.65%)
Recruitment	27 (33.33%)
Methods: Data collection, management, and analysis	
Data collection methods	80 (98.77%)
Data management	77 (95.06%)
Statistical methods – statistical methods for primary and secondary outcomes	75 (92.59%)
Statistical methods – additional analyses	49 (60.49%)
Statistical methods – missing data	3 (3.70%)
Ethics and dissemination	
Research ethics approval	73 (90.12%)
Protocol amendments	3 (3.70%)
Consent or assent	73 (90.12%)
Confidentiality	56 (69.14%)
Declaration of interests	40 (49.38%)

Access to data	21 (25.93%)
Dissemination policy – communication of results to participants	48 (59.26%)
Dissemination policy – author eligibility guidelines	10 (12.35%)
Dissemination policy – public access plans	1 (1.23%)
Appendices	
Informed consent materials	49 (60.49%)
Biological specimens	26 (32.10%)

4.3 SPIRIT Domain Scores

Table 3. Application of the SPIRIT 2013 to AOU studies: for each domain the correspondent measure of central tendency is reported.

Item	**Mean percentage**
Administrative information	55.70
Methods: Data collection, management, and analysis	70.13
Ethics and dissemination	48.52
	Median percentage
Introduction	75
Methods: Participants, interventions, and outcomes	66.67
Appendices	50
SPIRIT total	60.53

4.4 Comparative Analyses of Domain Scores

Table 4 shows, for each of the years considered, the mean score of each SPIRIT 2013 domain for variables with normal distribution and the median for variables with non-normal distribution.

While no statistically significant differences are evident over the years in the scores of the domains “Introduction,” “Methods: participants, interventions, and outcomes,” “Appendices,” and “Administrative information,” the ANOVA test detected a statistically significant difference between 2022 and 2023 in the scores of the domains “Methods: Data collection, management, and analysis” and “Ethics and dissemination.” In particular, an improvement in both scores can be observed, respectively from 68% to 71.16% (p-value = 0.048) for “Methods: Data collection, management, and analysis” and from 47.78% to 50.13% (p-value = 0.031) for “Ethics and dissemination.”

Table 4. Measures of central tendency for each domain of the SPIRIT 2013 by year.

	Year (mean %)		
Domain	**2021**	**2022**	**2023**
Administrative information	75	60	58.40
Methods: Data collection, management, and analysis	75	68	71.16
Ethics and dissemination	55.55	47.78	50.13
	Year (median %)		
	2021	**2022**	**2023**
Introduction	75	75	75
Methods: Participants, interventions, and outcomes	72.22	66.67	66.67
Appendices	50	50	50
SPIRIT totale	71.05	63.16	60.53

With regard to differences in SPIRIT 2013 domain scores according to study design (see Table 5), the ANOVA test showed statistically significantly higher scores for medical device studies compared to all other categories. Similarly, the test showed higher scores for observational studies with drugs compared to interventional studies, observational studies without drugs, and registries in the domains “Administrative information” (60% vs 50.79%; 60% vs 57.09%; 60% vs 50.79%) and “Ethics and dissemination” (55.56% vs 45.23%; 55.56% vs 48.66%; 55.56% vs 39.69%), as well as in the total SPIRIT 2023 score (63.16% vs 59.21%; 63.16% vs 60.53%; 63.16% vs 52.63%).

No other statistically significant differences were detected in domain scores according to study design.

Table 5. **Measures of central tendency for each domain of the SPIRIT 2013 by study design.**

Domain	**Study design (mean)**					
	Interventional	Observational with drug	Observational without drug	Registry	Study with biological samples	Study with medical device
Administrative information	50.79	60	57.09	50.79	50	70.37
Methods: Data collection, management, and analysis	74.29	66	71.03	65.71	71.67	76.67
Ethics and dissemination	45.23	55.56	48.66	39.69	50	59.26
	Year (median and IQR)					
Introduction	75	75	75	75	100	75
Methods: Participants, interventions, and outcomes	66.67	66.67	66.67	55.56	61.11	77.78
Appendices	50	50	50	0	100	50
SPIRIT totale	59.21	63.16	60.53	52.63	63.16	73.68

4.5 Correlation Analyses

In the evaluation of the correlation between the SPIRIT score (both for each domain and overall) and the number of years of research experience, a weak negative correlation emerged between the number of years of experience and the “Administrative information” domain (rho = −0.24; p-value = 0.032), while a weak positive correlation was observed between the number of years of experience and the variables “Methods: participants, interventions and analysis” (rho = 0.29; p-value = 0.021) and “Ethics and dissemination” (r = 0.31; p-value = 0.049).

A modest positive correlation was found between the number of publications of the study PI and the domains “Introduction” (rho = 0.12; p-value = 0.045) and “Methods: participants, interventions and analysis” (rho = 0.19; p-value = 0.034). Finally, interestingly, a positive correlation was observed between the number of publications and the total SPIRIT 2013 score, although not statistically significant (rho = 0.35; p-value = 0.62).

5. DISCUSSION

This thesis evaluated the presence of SPIRIT-related criteria and additional items in 81 interventional and observational study protocols developed at the Clinical Trials Center of Ospedale Maggiore di Novara. The results show that there is a consistent pattern among study protocols, they are methodologically well-reported but at the same time incomplete in governance, oversight, and operational transparency [10] [23].

The overall completeness rate (60.53%) indicates moderate protocol quality and suggests systematic gaps rather than isolated issues. The presence of key elements, such as objectives, outcomes, eligibility criteria, study design, data collection, and statistical analysis was reported in over 90% of protocols, reflecting strong attention to methodological rigor. In contrast, key operational and transparency elements were rarely documented, including protocol amendments (3.70%), handling of missing data (3.70%), sponsor roles (9.88%), authorship guidelines (12.35%), and public access plans (1.23%). These components are essential for ensuring compliance with Good Clinical Practice and safeguarding data reliability and transparency [21], similar deficiencies in protocol transparency have been previously reported, highlighting the importance of comprehensive protocol documentation for ethical oversight and reproducibility [23].

This imbalance suggests that protocols are often treated primarily as scientific descriptions rather than operational tools guiding study conduct and oversight [10]. This observation is consistent with previous analyses describing protocols as organizational tools that guide coordination, accountability, and standardization in clinical research [12].

Administrative and monitoring procedures may be assumed to be managed at the institutional level, leading to under-documentation of governance processes [18].

Both observational and interventional studies demonstrated strong methodological reporting, while governance and monitoring elements were more frequently documented in interventional and medical device studies. Although this may reflect stricter regulatory requirements and higher perceived risks [7], limited reporting of governance elements in observational studies and registry studies cannot be fully justified by lower risk, as even minimal risk studies require clear procedures for data integrity and participant follow-up [18].

Medical device studies achieved the highest overall completeness scores, while observational studies involving drugs demonstrated higher scores in administrative and ethics domains. This pattern may reflect stricter regulatory frameworks and documentation requirements associated with device and drug research.

The predominance of observational studies in the institutional research portfolio reflects real-world research practices and supports the need for developing a structured guideline beyond interventional trial frameworks. Although SPIRIT was originally developed for randomized trials, many of its items address universal aspects of Good Research Practice [11].

At the time of this study, no widely accepted checklist was available for the prospective development of observational study protocols. In contrast, the STROBE statement improves reporting of completed studies but does not guide protocol development [18]. The adapted SPIRIT framework helped address an important methodological gap.

The distribution of protocols across clinical departments, with higher representation from Cardiology and Clinical Biochemistry, reflects the variation in research activity within the institution.

Some departments appear to be more research active or better supported, which may influence how protocols are developed and documented. Differences in research culture, infrastructure, and administrative support across departments could help in explaining the observed variability in protocol completeness.

A slight but statistically significant improvement between 2022 and 2023 in data management and ethics-related domains suggests increasing institutional awareness of data governance and transparency requirements [23], even though overall completeness is still moderate. The decrease in administrative completeness over time may indicate increasing workload or poor administrative support, further emphasizing the need for standardized templates.

Despite the high level of investigator experience, there were weak associations observed between researcher characteristics and protocol completeness, suggesting that documentation gaps are unlikely to reflect lack of expertise but rather an absence of standardized institutional guidance.

This study has several advantages, including the use of recent protocols reflecting real institutional practice and item-level evaluation enabling domain comparisons.
On the other hand, this study has several limitations include the single-center design, which may limit the applicability of the findings, the focus on documented protocol content rather than actual study conduct because some procedures might be implemented in practice but not explicitly documented in the protocols, also the limited number of protocols in some study design categories may have reduced the statistical power.

Furthermore, the absence of a universally accepted checklist for non-experimental studies required adaptation of the SPIRIT framework, this adaptation may not fully capture the specific features of different study designs.

The findings have important institutional implications. Implementing an adapted SPIRIT-based checklist could standardize protocol development, reduce variability across departments, and improve the efficiency of ethics review. Improving protocol completeness should be viewed not only as an administrative requirement but also as a strategy to strengthen research reliability and accountability. The development of standardized protocol templates may enhance documentation quality, reduce review delays, and minimize implementation errors, particularly in observational and low-risk studies.

Future research should validate the adapted framework in different settings and assess the impact of standardized templates on protocol quality and review timelines. The recent release of SPIRIT 2025 and SPIROS 2025 guidelines provides an opportunity to repeat this analysis using updated, design-specific standards, future analyses could also incorporate protocols from 2024 and 2025 to evaluate longer-term trends.

In conclusion, clinical study protocols at the CTC are scientifically robust but show consistent gaps in governance, transparency, and operational planning. Standardizing protocol development represents a practical strategy to improve completeness, reduce variability, and strengthen the overall quality and credibility of institutional clinical research.

6. CONCLUSION

This thesis aimed to evaluate the completeness of clinical study protocols developed at the Clinical Trials Center of Ospedale Maggiore di Novara using an adapted SPIRIT-based framework applicable to both interventional and observational studies. The results shows that scientific and methodological aspects are generally well documented, while the governance, monitoring, and transparency are insufficiently reported.

These results show that gaps in protocol completeness are related to institutional documentation practices rather than lack of scientific expertise, highlighting the need for more consistent and structured guidance across departments and study designs.

The study provides practical value by proving that an adapted SPIRIT-based checklist can identify structural weaknesses and support the development of standardized protocol templates. Such measures may improve documentation quality, facilitate ethics review, and enhance the reliability of clinical research, particularly in observational and low-risk studies.

Future evaluations using SPIRIT 2025 and SPIROS 2025, including protocols from 2024–2025, may help monitor progress and support continuous improvement in protocol development.

Finally, strengthening governance, monitoring, and operational planning in study protocols represents a great opportunity to improve the quality of clinical research within the institution.

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