臨床試驗研究計畫書撰寫與審查重點 - 從原則到實踐

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為何計畫書是試驗的「憲法」？

在臨床研究的浩瀚工程中，有一份文件如同國家的“憲法”，一切行動皆以其為準則——它就是臨床試驗方案（Protocol）。

Research protocol

- It is a document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project.

What is a Clinical Protocol

- The protocol is a document that describes how a clinical trial will be conducted (the objective(s), design, methodology, statistical considerations and organization of a clinical trial,) and ensures the safety of the trial subjects and integrity of the data collected.

Why do we need a Protocol?

- Why do we need one?
  - Scientific validity
  - Subject safety
  - Replicate the science if necessary
  - Regulatory requirements

Functions of Clinical Trial Protocol

Guideline for the ***conduct*** of the trial

Quality control for all aspects of a clinical trial

To provide guidelines to the ***monitoring*** groups such as: IEC / IDMC.

Functions of Clinical Trial Protocol

Written agreement between:	***Legal documents*** for	To procure ***funding***
• the investigator • the participant, • and the scientific community	• **TFDA** and other regulatory bodies	

According to the ICH Good Clinical Practice guidelines, a protocol should include the following topics:

- Title Page (General Information)
- Background Information
- Objectives/Purpose
- Study Design
- Selection and Exclusion of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Adverse Events

According to the ICH Good Clinical Practice guidelines, a protocol should include the following topics:

- Discontinuation of the Study
- Statistics
- Quality Control and Assurance
- Ethics
- Data handling and Recordkeeping
- Publication Policy
- Project Timetable/Flowchart
- References
- Supplements/Appendices

Learn more at:
https://hub.ucsf.edu/protocol-development

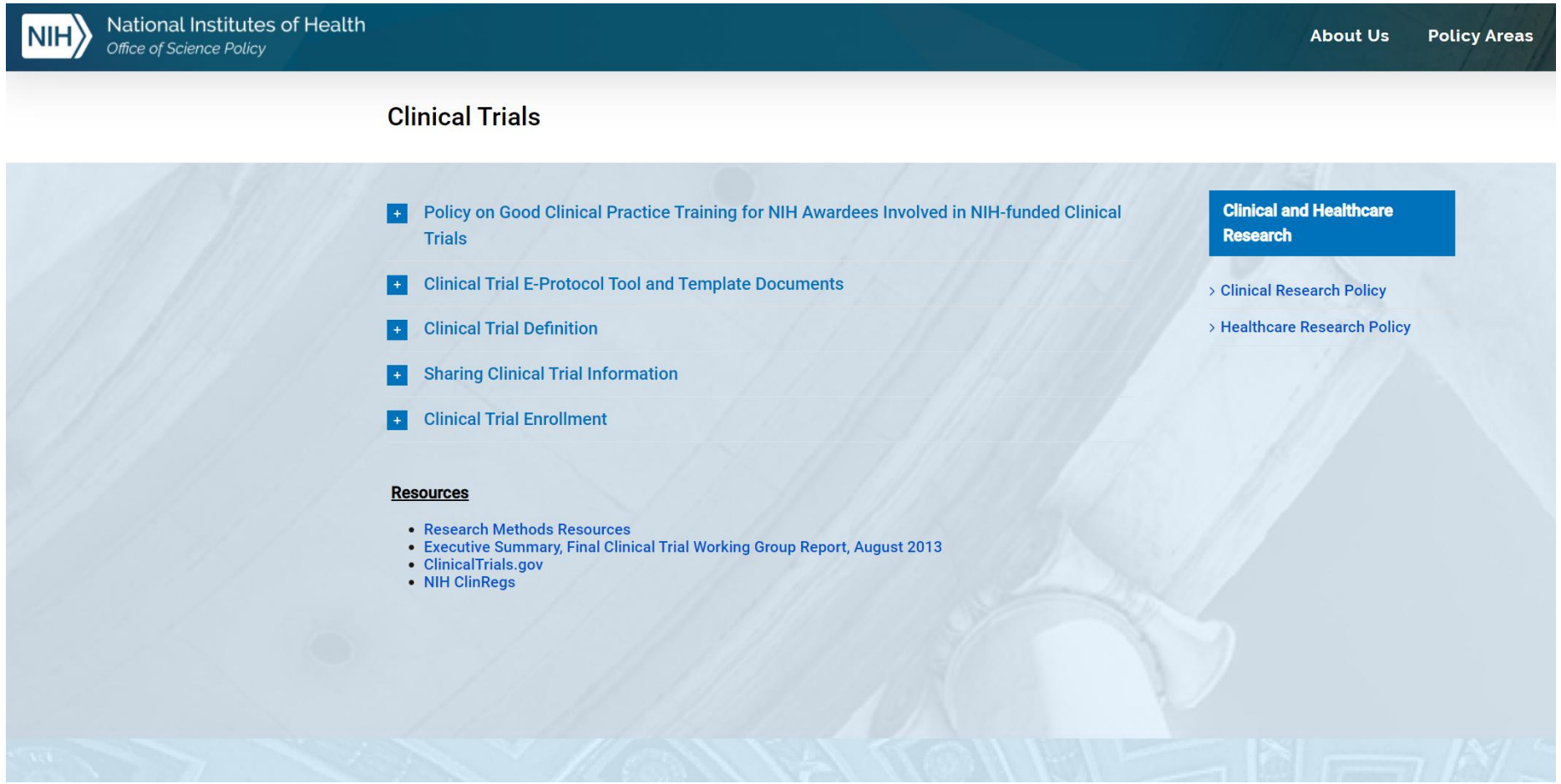
Sample Protocol Templates and Resoruces

Sample Protocol Templates and Resources:

- UCSF Protocol Template
- MOP Template
- UCSF Descriptive Study Protocol Template - The protocol template is a tool to help facilitate the development of protocols for retrospective chart reviews.
- DMID-Minimal Risk Template
- NIDCR-Interventional Protocol Template (Drug, Device, Behavioral)
- DMID- Greater Than Minimal Risk Template
- DMID- Interventional Template
- NIAID Clinical Research Toolkit- Clinical Trials Protocol Templates
- NCI-CTEP Protocol Development Templates and Guidelines
- Patient Care Manager Support Letter for Research

Protocol development assistance covering a wide-range of therapeutic areas is available. For cancer research protocol templates and additional guidance, please see Cancer Center Investigational Trials Resource Forms.

Learn more at:
https://osp.od.nih.gov/clinical-research/clinical-trials/



NIH– IND/IDE Word Template

Clinical E-Protocol Writing Tool

Benefits of the *e-Protocol Writing Tool* include:

- enables participation for multiple writers and reviewers
- allows assignments for writers and collaborators
- tracks progress and ensure document version control

The use of these templates is recommended, but not required.

Word Templates

Word versions of the protocol templates can also be downloaded for use outside of the e-protocol Writing Tool.
The following templates provide a common protocol structure and organization which can facilitate protocol review by oversight entities.

Protocol	Description	Word Template
Phase 2 and 3 Clinical Trials that Require FDA-IND or IDE Application	This protocol template aims to facilitate the development of two types of clinical trials involving human participants. The first type of trials are Phase 2 and 3 clinical trial protocols that require a Food and Drug Administration (FDA) Investigational New Drug (IND) or Investigational Device Exemption (IDE) application.	IND/IDE Protocol Word Template
Behavioral and Social Science Research (BSSR) Involving Humans	NIH developed a second protocol template to help behavioral and social science researchers prepare research protocols for human studies measuring a social or behavioral outcome or testing a behavioral or social science-based intervention.	BSSR Protocol Word Template

Applicants conducting phase 2 or 3 clinical trials that require Investigational New Drug applications (IND) or Investigational Device Exemption (IDE) applications can use an NIH-FDA template

<Title>

The title should be easy to remember, recognizable by administrative support staff, and sufficiently different from other protocol titles to avoid confusion. Brevity with specificity and neutrality is the goal. If there is a "short title" (e.g., an abbreviation used to refer to the study title, include here and that can be used throughout this document in place of the full title).

Protocol Number: < Number>

National Clinical Trial (NCT) Identified Number: <Number, if available>

Principal Investigator: < Principal investigator>

<IND/IDE> Sponsor: <Sponsor name, if applicable>

Sponsor means an individual or pharmaceutical or medical device company, governmental agency, academic institution, private organization, or other organization who takes responsibility for and initiates a clinical investigation.

NIH– IND/IDE Word Template

1 PROTOCOL SUMMARY

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

1.1 SYNOPSIS

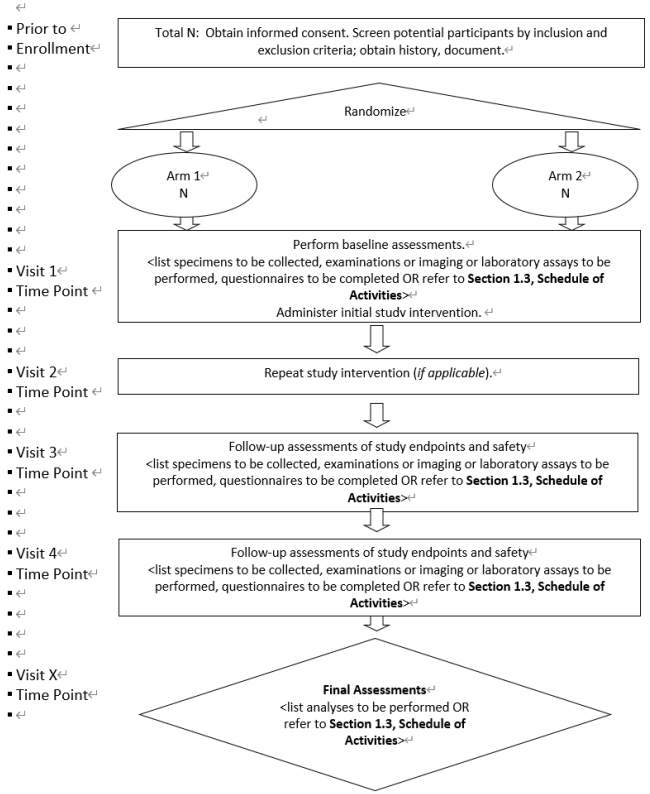
Title:	<Full title>
Study Description:	*Provide a short description of the protocol, including a brief statement of the study hypothesis. This should be only a few sentences in length. A detailed schematic describing all visits and a schedule of assessments should be included in the* ***Schema and Schedule of Activities, Sections 1.2 and 1.3,*** *respectively.*
Objectives:	*Include the primary and secondary objectives. These objectives should be the same as the objectives contained in the body of the protocol. These align with Primary Purpose in clinicaltrials.gov[1].*
	<Primary Objective:
	Secondary Objectives: >
Endpoints:	*Include the primary endpoint and secondary endpoints. These endpoints should be the same as the endpoints contained in the body of the protocol. These align with Outcome Measures in clinicaltrials.gov.*
	<Primary Endpoint:
	Secondary Endpoints: >

NIH– IND/IDE Word Template

Study Population:	*Specify the sample size, gender, age, demographic group, general health status, and geographic location.*
Phase:	<2 or 3 or N/A> *Phase applies to drugs and biologics*[2].
Description of Sites/Facilities Enrolling Participants:	*Provide a brief description of planned facilities/participating sites enrolling participants. Indicate general number (quantity) of sites only and if the study is intended to include sites outside of the United States.*
Description of Study Intervention:	*Describe the study intervention. If the study intervention is a drug or biologic, include dose and route of administration. For devices, provide a description of each important component, ingredient, property and the principle of operation of the device.*
Study Duration:	*Estimated time (in months) from when the study opens to enrollment until completion of data analyses.*
Participant Duration:	*Time (e.g., in months) it will take for each individual participant to complete all participant visits.*

Flow diagram

Example #1 Flow diagram *(e.g., randomized controlled trial)*



1.3 SCHEDULE OF ACTIVITIES (SOA)

The schedule below is provided as an example and should be modified as appropriate.

The schedule of activities must capture the procedures that will be accomplished at each study visit, and all contact, with study participants e.g., telephone contacts. This includes any tests that are used for eligibility, participant randomization or stratification, or decisions on study intervention discontinuation. Only include procedures that contribute to participant eligibility and study objectives and endpoints. Other procedures should be done sparingly and with consideration, as they may add unnecessary complexity and detract from recruitment.

Allowable windows should be stated for all visits. To determine the appropriate windows, consider feasibility and relevance of the visit time points to study endpoints (e.g., pharmacokinetic (PK) studies may allow little or no variation, with required time points measured in minutes or hours, whereas a 6-month follow-up visit might have a window of several weeks).

Procedures	Screening Day -7 to -1[a]	Enrollment/Baseline Visit 1, Day 1[a]	Study Visit 2 Day 7 +/-1 day[a]	Study Visit 3 Day 14 +/-1 day[a]	Study Visit 4 Day 21 +/-1 day[a]	Study Visit 5 Day 28 +/-1 day[a]	Study Visit 6 Day 35 +/-1 day[a]	Study Visit 7 Day 42 +/-1 day[a]	Study Visit 8 Day 49 +/-1 day[a]	Study Visit 9 Day 56 +/-1 day[a]	Study Visit 10 Day 63 +/-1 day[a]	Study Visit 11 Day 70 +/- 1 day[a]	Study Visit 12 Day 77 +/-1day[a]	Final Study Visit 13 Day 84 +/-1 day[a]
Informed consent	X													
Demographics	X													
Medical history	X													
Randomization	X													
Administer study intervention		X			X			X			X			
Concomitant medication review	X	X----------												X
Physical exam (including height and weight)	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
serum chemistry [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [b]	X													
EKG (as indicated)	X													
Adverse event review and evaluation	X	X----------												X
Radiologic/Imaging assessment	X				X				X					X
Other assessments (e.g., immunology assays, pharmacokinetic)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium.

b: Serum pregnancy test (women of childbearing potential).

Inclusion Criteria

[In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged <specify range>
4. In good general health as evidenced by medical history or diagnosed with <specify condition/disease> or exhibiting <specify clinical signs or symptoms or physical/oral examination findings>
5. <Specify laboratory test> results between <specify range>
6. Ability to take oral medication and be willing to adhere to the <study intervention> regimen
7. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional <specify duration> weeks after the end of <study intervention> administration
8. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner
9. Agreement to adhere to Lifestyle Considerations (see section 5.3) throughout study duration]

Exclusion Criteria

[An individual who meets any of the following criteria will be excluded from participation in this study:

1. Current use of < specify disallowed concomitant medications>
2. Presence of <specific devices (e.g., cardiac pacemaker)>
3. Pregnancy or lactation
4. Known allergic reactions to components of the <study intervention>, <specify components/allergens>
5. Febrile illness within <specify time frame>
6. Treatment with another investigational drug or other intervention within <specify time frame>
7. Current smoker or tobacco use within <specify timeframe>
8. < Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>]

NIH – Clinical e-Protocol Writing Tool

https://e-protocol.od.nih.gov/#/home

NIH – Clinical e-Protocol Writing Tool

Collaborate and Write

Use the NIH e-Protocol tool to author protocols relating to Phase 2 and 3 IND-IDE studies as well as behavioral and social sciences research involving humans. Collaborate with writers and reviewers by assigning them to protocol sections.

Track Progress

Track writing and reviewing progress of your protocol. Email notifications will alert your team when a protocol section is ready for review.

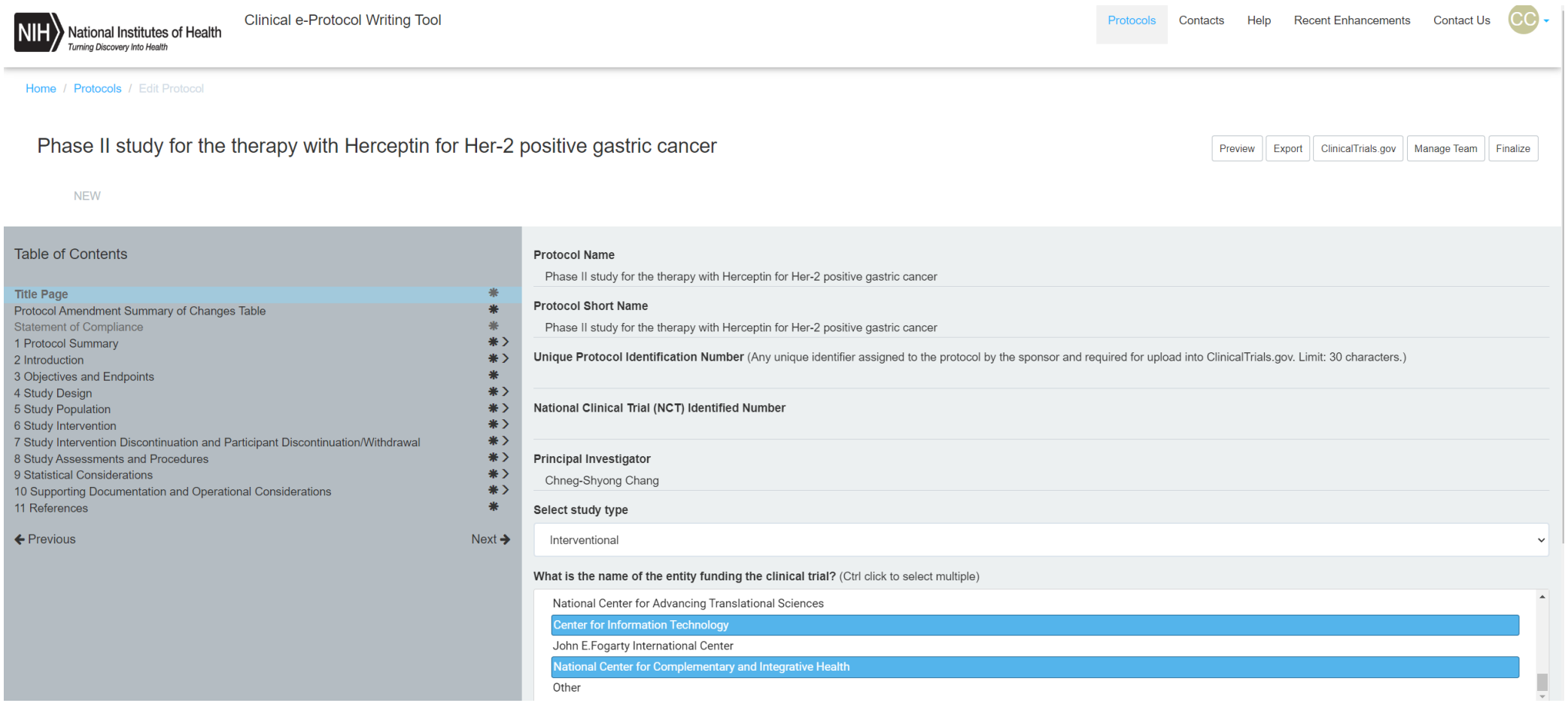
Export Protocol

When writing is finished, export your complete and final protocol document for external reviews, including to ClinicalTrials.gov.

About

The electronic protocol writing tool aims to facilitate the development of *Phase 2 and 3 IND/IDE Clinical Trial Protocol Template* as well as the *Behavioral and Social Sciences Research Involving Humans*. The tool has been developed through the National Institutes of Health (NIH) Office of Science Policy.

NIH – Clinical e-Protocol Writing Tool



一份設計縝密、撰寫清晰的方案是：

- 受試者安全的終極保障：它預設了所有可能的風險及因應措施。
- 資料品質與完整性的基石：統一的操作流程（SOP）是避免方案偏離（Protocol Deviation）的關鍵。
- 研究能否回答科學問題的決定因素：錯誤的設計無法透過統計分析來彌補。
- 與審查機構（IRB/EC、監管機構）高效溝通的載體：一份問題百出的方案會導致多次質詢，嚴重拖慢啟動時間。

核心主題一：方案撰寫的「雷區」與最佳實務

研究背景與目的：切忌「大而空」

- 雷區：文獻堆砌，未能清楚闡述未滿足的臨床需求和研究的創新點。
- 審查重點：立題依據是否充分？本研究是否必要？（避免重複性研究）
- 最佳實踐：
  - 用數據說話：例如，「目前標準治療的有效率僅為40%，且存在XX毒性」。
  - 目的撰寫遵循SMART原則（Specific, Measurable, Achievable, Relevant, Time-bound）。
  - 主要終點必須直接、有力地回答最核心的科學問題，且與監管機構認可的終點一致（如OS, PFS, ORR等）。

研究設計：選擇的藝術與科學

- 雷區：設計選擇不當（如該用雙盲安慰劑對照卻用了開放設計）、分期不清（I/II期？）、隨機化與盲法描述模糊。
- 審查重點：設計是否最適合回答研究問題？是否最大限度地控制了偏倚？
- 最佳實踐：
  - 明確說明是前瞻性/回顧性、介入性/觀察性、隨機/非隨機、平行分組/交叉設計、優效性/非劣效性/等效性檢定。
  - 詳細描述隨機化方法（區組隨機？分層因素？）和盲法設定（誰被設盲？破盲流程？）。

受試者選擇：入排標準的「精準刀法」

- 雷區：標準過於寬泛或嚴苛，使用模糊術語（如「嚴重肝腎功能不全」），缺乏可操作性。
- 審查重點：風險受益比是否合理？目標群體是否定義清晰？是否公平公正？
- 最佳實踐：
  - 入選標準：聚焦於最能從介入中獲益的族群。
  - 排除標準：著重於保護高風險族群（如孕婦、有合併症者）和保證資料品質（如排除無法按時訪視者）。
  - 量化！量化！量化！ ：將「肝功能不全」改為「ALT/AST > 2.5倍正常值上限（ULN）」。

干預措施：細節是魔鬼

- 雷區：給藥方案、劑量調整、允許/禁止的合併用藥描述不清楚。
- 審查重點：是否可安全、一致地執行？
- 最佳實踐：
  - 像說明書一樣精確：藥物名稱、劑量、途徑、頻率、療程、配置方法、保存條件。
  - 必須包含劑量調整和暫停給藥的原則（如出現3級非血液學毒性如何處理）。
  - 明確定義禁止的合併用藥及洗脫期。

流程圖與評估流程：讓時間軸一目了然

- 最佳實踐：
  - 強烈建議使用「試驗流程圖」：篩檢期、治療期、追蹤期，各時間點需進行哪些手術（訪視、檢查、給藥、資料收集）。
  - 明確訪視窗口期（如Day 1 ± 3 days），增強可行性。

統計：樣本數與方法的「定海神針」

- 雷區：樣本量計算無依據或參數設定不合理；統計分析方法與資料類型不符。
- 檢討重點：是否具備足夠的檢驗效能（Power）？分析方法是否科學？
- 最佳實踐：
  - 樣本量計算：必須明確提供α值、power、效果值（Effect Size）的估計依據、計算公式或軟體名稱。
  - 統計分析集：明確定義全分析集（FAS）、符合方案集（PPS）和安全性集（SS）。
  - 詳細列出：每個終點將使用的特定統計檢定方法（如，主要終點以log-rank檢定和Cox比例風險模型）、缺失資料處理方法、亞組分析計畫。

核心主題二：審查委員的「火眼金睛」在看什麼？

科學評論 (Scientific Review)

- 核心問題：“這個研究設計能否清晰、嚴謹、有效率地回答它所提出的科學問題？”
- 關注點：創新性、設計合理性、終點選擇、統計方法。

倫理審查 (Ethical Review)

- 核心問題：“受試者的權益、安全和福祉是否得到了最大程度的保護？”
- 關注點：
  - 風險受益比：風險是否最小化？受益是否合理？是否有獨立的資料安全監查委員會（DSMB）？
  - 知情同意流程：知情同意書（ICF）是否完整、易懂？獲取過程是否符合規定？
  - 受試者選擇：是否公平？對弱勢族群的保護是否充分？
  - 保密與補償：隱私權保護措施是否到位？受測者補償/賠償是否合理？

合規與可行性檢討 (Compliance & Feasibility)

- 核心問題：“本研究是否符合GCP和監管法規？是否在現實中可行？”
- 關注點：
  - 方案是否遵循ICH-GCP、赫爾辛基宣言及地方法規？
  - 研究者團隊是否有足夠資質、經驗及資源（病患池、設備）在預定時間內完成招募？
  - 方案流程是否過於繁瑣，導致依從性低和高脫落率？

黃金法則回顧

- 1. 精準原則：消滅模糊詞彙，一切皆可量化、可測量。
- 2. 前瞻性原則：預判所有可能的風險和操作問題，並制定預案。
- 3. 一致性原則：方案全文、ICF、CRF等所有文件的資訊必須高度一致。
- 4. 合規原則：時刻以ICH-GCP為綱，確保倫理和監管合規。
- 5. 可行性原則：站在執行者（研究者、CRC）的角度思考，方案是否「接地氣」？

最後的建議

- 善用清單：在提交前，使用SPIRIT 2013聲明的檢查清單進行自查。
- 內部預審：邀請資深同事、統計師、CRC從不同角度進行內部預審。
- 擁抱回饋：將倫理委員會和監管機構的質詢視為優化方案、避免後續更大問題的寶貴機會。

Q & A