Teva Investigator-Sponsored Study (ISS) Handbook for Sponsor-Investigators

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1. Introduction

Teva supports research that will further the understanding of our products, disease entities and their treatments. A researcher can submit their own study proposals for consideration involving specific research or a particular treatment for a specific patient population.

In this handbook, you will be provided the key aspects of engaging with Teva as a sponsor-investigator (SI) in an Investigator Sponsored Study (ISS), including your expected responsibilities in performing successful research as well as what you can expect from Teva. Note, if your research is approved for support, this document does not replace a signed agreement.

Before you submit your independent research to Teva, make sure you can follow local, regional and global regulations as well as understand your responsibilities as both an investigator and sponsor and that you have adequate staff and facilities to conduct the research effectively and efficiently.

In this handbook you will also receive instructions for submitting an ISS application including background on the Teva review and approval process.

2. What is an ISS?

An Investigator Sponsored Study (ISS) is an independent scientific investigation initiated and conducted by a non-Industry investigator who assumes all study sponsor responsibilities as defined by applicable laws and regulations.

An ISS, maybe be known by many names including:

- Investigator Initiated Study (IIS)
- Investigator Initiated Trial (IIT)
- Investigator Sponsored Trial (IST)

Types of ISS:

Your ISS may be any one of the following types of clinical, pre-clinical or non-clinical studies:

- screening/diagnostic
- interventional
- non-interventional

- retrospective
- prospective
- epidemiological
- health economic or outcomes research

3. Sponsor-Investigator

The investigator (clinical researcher) is responsible for both sponsor and investigator's responsibilities. Therefore, the role is called "Sponsor-Investigator" (SI).

The SI must have the necessary expertise, qualifications, authorizations and operational capacity to conduct the study.

The SI is responsible for study design, conduct, monitoring, training, archiving, administration, and adherence to all regulatory and ethics requirements, including but not limited to Good Clinical Practice (GCP), and Good Pharmacovigilance Practices (GVP), safety reporting, study registration (as applicable), study results reporting and publication(s).

Note: Representatives of Teva are not involved in developing, designing, or writing the concept and/or protocol for an ISS and must not be involved in submitting an ISS concept and/or protocol through the Teva ISS portal, also known as the Submission Management system (SMS). If you experience technical issues, contact Teva for technical support.

Appendix 1 provides a list of Sponsor-Investigator responsibilities for your review and consideration before you decide to fulfill the role of a SI. While this is not a comprehensive list, it provides a good example of what SI responsibilities may be. Before submitting your research please review this to ensure you can fulfill the responsibilities of a SI.

4. Regulatory Requirements

Before you submit an ISS proposal, make sure you are familiar with the requirements for both a sponsor and an investigator including but not limited to the following:

- Local regulations
- Code of Federal Regulations, CFR, Title 21 Chapter I Subchapter A Part 50.3
- Code of Federal Regulations, CFR, Title 21 Chapter I Subchapter D Part 312
- ICH, GCP (E6)

While all regulatory obligations including study monitoring are the responsibility of the Sponsor-Investigator, Teva will retain the right to audit your site and study during and after the study. Additionally, you must immediately notify Teva of any inspections as soon as you become aware.

5. Teva's ISS Support

As a SI you may request that Teva supports your research with funding and/or supply of product.

Teva has the responsibility to evaluate your submission, review it and approve or decline the ISS submission. If the submission is approved for support, Teva will work with you to establish an ISS agreement as well as provide the support requested (funding and/or drug).

6. Submitting an ISS Request to Teva

If you wish to propose an ISS for Teva's consideration, you must submit your proposal via the Teva ISS Submission Management System.

Below you will find links to a Job Aid on how to create your profile and submit an ISS in the Teva Submission Management System (SMS) portal:

- Link to the submission process information:
  Teva Collaborative Research (CR) and Investigator Sponsored Study (ISS) registration and submission Job Aide
  Note: The SMS portal is for the submission of Investigator-Sponsored Studies as well as Collaborative Research. Please ensure you select the correct option.
- The link to the Teva Submission Management System portal:
  Teva ISS intake portal

The Teva ISS review process is a two-step process. First, you will submit your ISS concept. The Teva Investigation Review Committee or IRC, will review your submission. If the (IRC) determines there is interest, you will be asked to submit a full protocol. Regardless, of the committee decision, you will receive a communication either providing the steps to submit a full protocol or a message that your proposal has been declined.

If you are asked to submit a full protocol, please note, this is not an approval. A full protocol must be reviewed by the IRC. If the protocol is approved for support by the IRC you will receive a communication regarding next steps. If your submission is declined for support, you will receive a communication confirming this as well.

The details of what is required for each submission is listed below.

ISS proposal's content:

You will be asked to include with your submission the following:

- Curriculum Vitae (CV) (ensure the CV in your profile is updated in the system)
- Valid medical license, as applicable (ensure the copy of your valid license is attached to your profile in the system)
- Study details including timelines, budget, drug requests, and concepts or protocols, include the following elements:

ISS concept submissions:	ISS protocol submissions:
• Brief Background/Rationale • Type of Data Collection • Retrospective or Prospective • Primary and Secondary Objectives • Primary and Secondary variables • Study design • Major Inclusion Criteria • Major Exclusion Criteria • Planned Number of Patients • Study Duration • Planned Number of sites • Rate of enrollment • Patient Population • Primary Efficacy Variables • Secondary Efficacy Variables • Statistical methods • Sample size calculation • High-level timeline [First Patient In (FPI), Last Patient Out (LPO), Clinical Study Report] • Publication Plan	• Background/ Rationale • Type of Data Collection • Retrospective or Prospective • Primary and Secondary Objectives • Significance • Hypothesis • Methods • Inclusion Criteria • Exclusion Criteria • Planned number of patients • Expected rate of enrollment • Study duration per patient • Planned number of sites • Population • Indication • Primary Efficacy Variables • Secondary Efficacy Variables • Safety Variables • Design • Statistical Methods

• Study drug (dosage and quantity)
• Matching Placebo (quantity)
• Budget Total Estimate and/or Detailed Budget
	• Sample Size Calculations
	• Timelines [First Patient In (FPI), Last Patient Out (LPO), Clinical Study Report]
	• Detailed Budget (To accompany protocol submission, as applicable based on study design)
	  ○ Costs calculated on a per-subject basis
	  ○ Start-up fee
	  ○ Independent review board (IRB) fees
	  ○ Overhead costs
	  ○ Breakdown of hourly fees for staff and/or equipment time
	  ○ Cost of tests and/or supplies
	  ○ Medical writing fees, presentation and/or publication fees – note: these items cannot be added to the budget after the contract is final
	  ○ Breakdown of any fees included in the budget

7. Budget and Protocol Amendments

Teva can only consider funding requests that cover study-related costs and are within Fair Market Value. Teva can only process invoices based on work performed and as per the finalized ISS agreement.

Any requests to increase the budget or a non-administrative protocol amendment, must be submitted to Teva for review and approval via the IRC. IRC approval must be obtained and ISS Agreement should be amended as applicable.

If Teva is providing funds for the research, any unused funds must be returned to Teva at the conclusion of the study.

8. Product support

If Teva will be providing product for your ISS, you will be responsible for the product management activities such as labeling, relabeling (if required), randomization schema, as well as maintaining the control of the product including inventory controls and proper storage and administration.

Any product remaining at the end of the study must be either destroyed on site, disposed of per regulations or directly returned to Teva as in accordance with the ISS agreement.

9. Periodic Study Updates

Once an ISS is approved, Teva utilizes TGEC (Teva Global eTrial Master File and Clinical Trial Management System) to communicate with you about your ISS. If your ISS is approved, you will be required to update your study as well as submit any budget or protocol changes through this system.

Please note, this system is used for study, enrollment and milestones updates as well as a repository for study documents. It is not used for the study Trial Master File. As the sponsor of the study, you will be responsible for creation and maintenance of the TMF and all required study documents outside of TGEC.

Clinical Operation Milestones:

As the Sponsor-Investigator, the expectation is you will provide timely and accurate study updates, via TGEC, at set intervals per the ISS agreement. This is usually at minimum, once a quarter.

You will be reporting on key study elements such as:

- Enrollment updates
- Critical study milestones such as:
    - First study Patient Screened
    - First study Patient In / Start of Data Collection
    - Last study Patient In
    - Last Patient Out / End of Data Collection
    - Database Lock
    - Clinical Study Report/Final Study Report Approval & Delivered / Study Completion

You will also be expected to ensure requested, required and most up-to-date ISS documents are uploaded into TGEC.

Teva expectations are that your updates are timely, accurate and logical. If your updates are not completed as such your study will be in jeopardy of termination of support. Examples of items that could lead to early termination of Teva support:

- Not meeting obligations as specified in the ISS agreement
- Not meeting timelines
- Missed or extended milestones
- Not providing progress reports on time and through the TGEC

TGEC access and training:

You will be provided training prior to gaining access to the TGEC system. Once granted access, you will also have Job Aid to assist with system utilization.

As the Sponsor Investigator, you will be expected to complete this training and gain access to the system. Relevant research staff (e.g., sub-investigators, clinical research coordinators) may also request access as needed.

10. Study Records Retention

As the SI, you will be required to maintain complete and accurate records related to the Study, in accordance with the ICH/GCP Guidelines, other applicable regulations and in accordance with the Teva ISS agreement. As the Sponsor of the study, you are responsible to ensure documentation is collected and maintained.

11. Study Reports and Publications

Upon completion of the Study, the expectation is the data will be published.

You will be required to send the draft publication to Teva for a medical accuracy review and according to the conditions as noted in the ISS agreement.

Draft publications and abstracts should be uploaded to the TGEC system for Teva review per the timelines established in the ISS agreement.

Teva will provide the medical accuracy review and may provide feedback as detailed in the ISS agreement. Teva will also require disclosure of Teva support in any publication.

Final study reports and publications should also be uploaded to the TGEC system when available.

Attachment 1: Investigator Sponsored Study

Examples of responsibilities:

Responsibility	Owner
General:	
Develop the study	Sponsor-Investigator
Sponsor of the study	Sponsor-Investigator
Data ownership	Sponsor-Investigator
Intellectual property	Teva
Selecting qualified investigators	Sponsor-Investigator
Selection and contract with any service providers	Sponsor-Investigator
Request of payment per ISS agreement	Sponsor-Investigator
Issuance of payment to Institution per milestone achievement and per ISS agreement	Teva
Study documents	
Developing, designing, or writing the concept and/or protocol	Sponsor-Investigator
Medical writing	Sponsor-Investigator
Study results reporting and publication	Sponsor-Investigator
Statistical analysis	Sponsor-Investigator
Study submissions:	
Submitting study concept and/or protocol in Teva portal	Sponsor-Investigator
Regulatory local submissions (EC, IRB, etc.)	Sponsor-Investigator
Maintaining an effective IND, if needed	Sponsor-Investigator
Investigational drugs:	
Shipment of drug to Sponsor-Investigator	Teva
Relabeling, if required	Sponsor-Investigator
Maintain control of Investigational product (includes inventory, storage, return or destruction)	Sponsor-Investigator
Safety:	
Protect the rights, safety, and welfare of subjects.	Sponsor-Investigator

Safety reporting to Teva (as per agreement) and to Health Authorities according to regulations	Sponsor-Investigator
Study conduct:	
Responsible for ensuring that informed consent is obtained	Sponsor-Investigator
Site monitoring	Sponsor-Investigator
Completion Quarterly updates (at minimum) in TGEC	Sponsor-Investigator