Chief Medical Office

Investigator Initiated Trials: a guide for prospective Investigators

NOVARTIS

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Novartis believes in the need to support ethical independent clinical research

Introduction

As part of the commitment by Novartis to deliver innovative therapies to patients worldwide, Novartis believes in the need to support ethical independent clinical research conducted by qualified third-party sponsors (Investigators). The value of this scientific research, together with Novartis-sponsored research, is fundamental to the understanding of the benefit/risk profile of Novartis therapies and the exploration of new opportunities to address unmet medical needs. This is why Novartis provides support to new Investigator Initiated Trials/Studies (IITs) every year.

An IIT is defined as a study with scientific and medical merit developed and sponsored by an independent Investigator or academic sponsor. An IIT is a clinical study conducted without the participation of Novartis, for which the IIT sponsor requests Novartis to provide either funding, drug product or both.

As an Investigator, if your IIT proposal is accepted, Novartis may provide you with financial support and/or Novartis product(s). However, you will retain full responsibility and control of the design, initiation, management, data analysis, monitoring, and reporting, as the sponsor of the study. Please note that for Non-Interventional Studies, Novartis is only able to provide financial support, not study drug.

The purpose of this guide is to provide a clear description of each of the essential requirements that must be fulfilled before support will be considered by Novartis, and to highlight your obligations as the study sponsor when your IIT is being supported by Novartis.

Requirements (feasibility) to conduct a clinical study

The following are the key requirements that will need to be fulfilled in order for Novartis to evaluate and consider supporting your study. Should you have any questions on these requirements, please contact your Novartis Medical Science Liaison (MSL) or local Medical contact.

All IIT submissions should be made to Novartis in GEMS, our cloud-based system which you can access through www.novartis.com.

Investigator qualifications

All of the following documents must be provided:

- A current curriculum vitae, to ensure that the Investigator is suitably qualified and able to conduct the required evaluation and analysis
- A current valid license to practice medicine*
- Recent clinical research experience within the previous 3 years*
- Good clinical practice (GCP) training within the previous 3 years*

**Only applicable for Interventional Studies*

Study Criteria

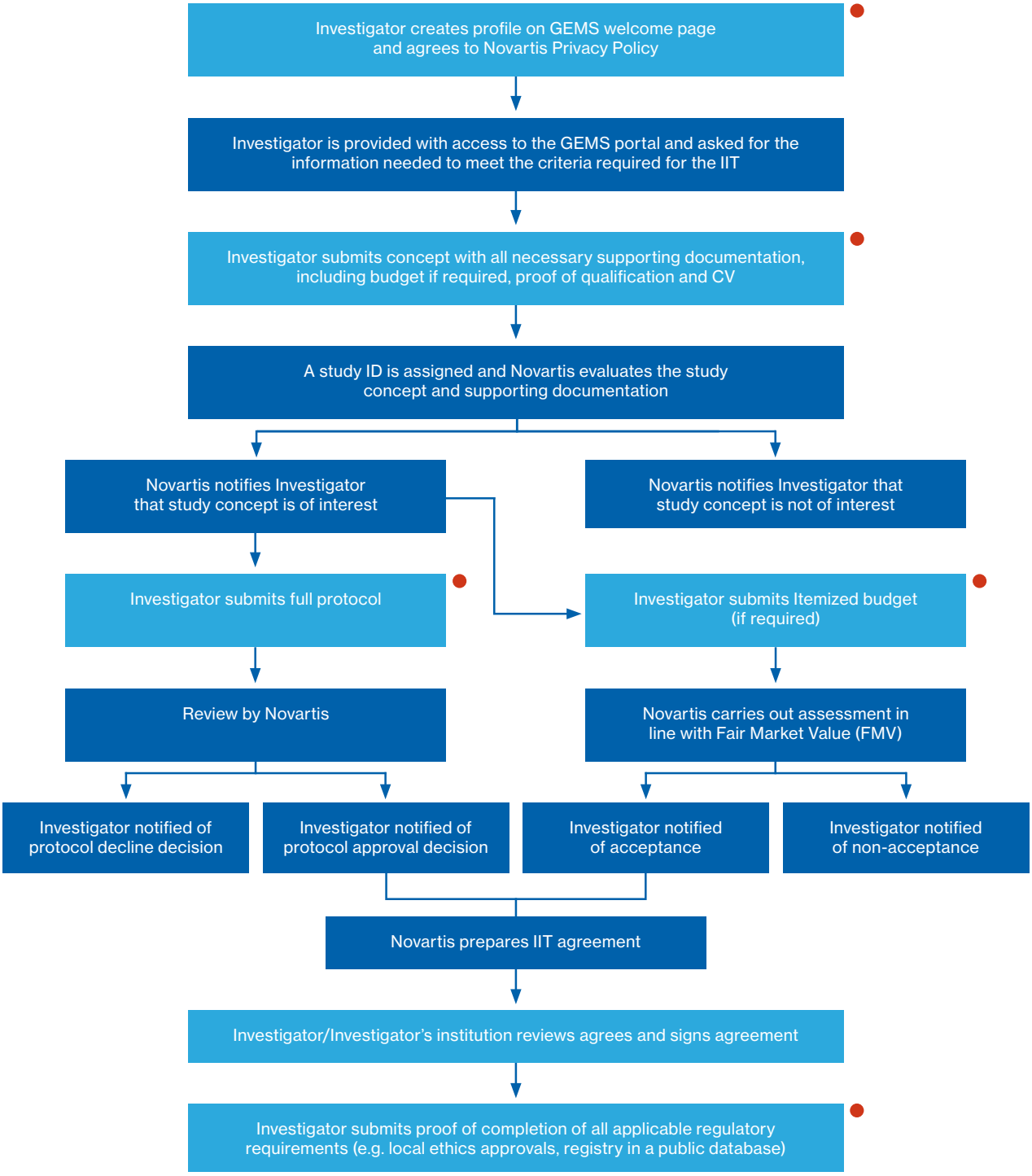
The proposed study should be for a legitimate research purpose, with scientific merit, and that complements Novartis-generated research to:

- Better understand the risk/benefit profile of the compound
- Address an unmet medical need
- Align with the Novartis compound scientific/ development strategy as indicated on www.novartis.com strategic areas of interest.

Resources

The Investigator must have the appropriate infrastructure in place and capability to conduct the study proposed.

Overview of the submission/application process



Key

Investigator

Novartis

● Denotes actions where Investigators will be required to submit and upload information and documentation associated with their IIT via the Novartis 'GEMS' portal. This portal manages each stage of a Novartis IIT, from initial concept submission through to final report and publication.

Overview of the IIT process

Receipt of funding/study drug

IIT budgets submitted to Novartis will be subject to a Fair Market Value (FMV) assessment against an externally benchmarked database prior to approval.

The purpose of IIT funds are only to further the scientific research and knowledge within a particular therapeutic area. IIT funds cannot be provided to just gain experience with a study drug or treatment protocol.

It is also important to note that IIT support may not be given to pay for the recipient's ordinary operating expenses (i.e. expenses of activities that the recipient is already required to perform or customarily performs) or support research that has already occurred. Following the initiation of a study, funding will be released as key milestones are achieved, in accordance with the payment schedule noted in the IIT Agreement. The mandatory key milestones include:

Milestone	Percentage of funding (%)
Execution of IIT Agreement, Ethics Committee (EC)/ Health Authority (HA) approval and First Patient First Visit (FPFV)*	**10%**
Provision of final Third-Party Study Report (TPSR) to Novartis	**10%**
Submission for publication or provision of publication to Novartis	**10%**

**5% can be paid on execution of the IIT Agreement*

Please note that all other payment milestones will depend upon the study design and the schedule noted in the IIT Agreement and could include milestones based on recruitment.

You will need to have the following items in place and provided to Novartis prior to release of study drug and/or funding:

- Final protocol (including version number and date)
- An institutional review board (IRB)/EC approval of the protocol and informed consent form
- HA approval (as applicable)
- Itemized study budget (subject to FMV assessment)
- Fully executed IIT Agreement with Novartis

Conducting the IIT

Study status, reporting and registry in a public database

According to the Novartis IIT Agreement, you should inform Novartis of any updates to the status of the IIT. For example:

i. You must verify that all applicable regulatory requirements have been met which includes clinical trial registration in a public database such as www.clinicaltrials.gov;
ii. You should provide enrollment data, confirming that safety information is being transferred to Novartis as required;
iii. As per the agreed frequency in the IIT Agreement, you should complete Adverse Event (AE) reconciliation and share the completed AE reconciliation summary form with Novartis;
iv. You should advise and provide Novartis with any amendment to the protocol.

Safety reporting requirements

One of the most important requirements of an IIT Investigator is the responsibility to monitor and report safety data to the appropriate authorities, in a timely and accurate manner.

In addition to reporting safety data to all relevant authorities, you will have the responsibility to report the following safety information to Novartis in accordance with the IIT Agreement.

These requirements will vary depending on whether the study is of an interventional or non-interventional nature, the type of data collection, as well as on whether the study is focused or not on a Novartis product. These are outlined below:

For Interventional Studies

Safety reporting requirements for interventional studies INVOLVING a Novartis investigational product
Transfer to Novartis in an ongoing manner of Serious Adverse Events (SAEs), reports of drug exposure during pregnancy and reports of drug misuse or abuse
Transfer to Novartis of any findings that might alter the current benefit-risk profile of the Novartis product or that would be sufficient to consider changes in the Novartis product administration or in the overall conduct of the study
Provision of the randomization codes (for blinded Interventional Studies)
Provision of copies of Investigator notifications for suspected unexpected serious adverse reactions (SUSAR) or provision of biannual SUSAR listing*
Provision of copies of Development Safety Update Reports*
Performing Adverse Event (AE) reconciliation periodically and at the end of the study

**If the preparation and submission of such documents are required as per local regulations*

Safety reporting requirements for interventional studies NOT INVOLVING a Novartis investigational product
Notification to Novartis of any Adverse Drug Reaction (ADR) (irrespective of seriousness) to a Novartis product that the Investigator becomes aware of as spontaneous reports

For Non-Interventional Studies

A Non-Interventional Study can involve:

- **Primary data collection,** for instance, prospective observational studies and registries in which the data collected derive from routine clinical care or scientific outcomes research

OR

- **Secondary use of data,** for instance, database research or review of records where all the events of interest have retrospectively occurred (e.g. case-control, cross-sectional and cohort studies)

The safety data requirements for each type of Non-Interventional Study are shown below:

The timelines for providing this information to Novartis may differ depending on where the study is being conducted according to local regulatory requirements. The timelines will be specified in the IIT Agreement.

In turn, Novartis will ensure that any important safety findings or urgent safety measures for the Novartis product that is the focus of the IIT are shared with the investigator. Novartis will also provide an output of the Novartis safety database for performing AE reconciliation, as required.

1. Involving Primary data collection and WITH a Novartis product of focus
Transfer to Novartis in an ongoing manner of SAEs, reports of drug exposure during pregnancy and reports of drug misuse or abuse
Transfer to Novartis of non-serious AEs suspected to be causally related to the Novartis product i.e. Adverse Drug Reactions (ADRs)
Transfer to Novartis of any findings that might alter the current benefit-risk profile of the Novartis product
Perform AE reconciliation periodically and at the end of the study

2. Involving Primary data collection but NO Novartis product of focus
Notification to Novartis of any ADR (irrespective of seriousness) to a Novartis product that the Investigator becomes aware of as spontaneous reports

3. Involving Secondary use of data
Transfer to Novartis of any findings that might alter the current benefit-risk profile of the Novartis product *Note: Individual AE reporting to Novartis is not required*

Study results and publications

In addition to local/international regulations, Novartis requires the final Third-Party Study Report (TPSR) to be provided within 13 months of the Last Patient Last Visit (LPLV) (or within 7 months in the case of pediatric trials) as outlined in the executed agreement. For TPSRs written in languages other than English, a full English translation is required for IITs that used a Novartis product.

As part of Novartis' commitment to publishing research, you are encouraged to publish the results of IITs. As the Investigator, the content of any publication is your responsibility, and Novartis will not be involved in authorship selection or writing and should not be included as a co-author of IIT publications.

You should submit any publications to Novartis for review at least 15-30 days prior to submission, depending on the publication type.

In order to receive the two final milestone payments, you must produce a TPSR within the specified timelines, as outlined in the executed agreement, and attempt submission of study data for publication, or provision of the publication to Novartis, e.g. journal, manuscript, abstract, or poster for a congress.

Overview of key responsibilities of Novartis and the Investigator

Responsibilities	Novartis	Investigator
Development of the Research Protocol		●
Review of the Research Protocol	●	
Distribution of updated, approved product information	●	
Submission of dossier to IRB/EC at study start and annual renewal		●
Submission of dossier to local HA		●
Registry of IIT in a public database, such as www.clinicaltrials.gov		●
Implementation and monitoring of clinical research (including data monitoring)		●
Contracting with third-party vendors (clinical research organizations, medical writing, Pharmacokinetic (PK) or other analyses, patient insurance, statistical, courier, etc.) and the management and oversight of any other participating sites or contractors		●
Conducting of research (patient inclusion, exams conduction, etc.)		●
Ensure that the IRB/EC/local HA approved protocol is adequately followed (in accordance with GCP, applicable guidelines and local and international standards)		●
Submission of protocol amendments		●
Review of protocol amendments	●	
Maintaining clinical records of the study and assurance of the veracity of collected data and other attributions related to GCP		●
Reporting of safety data to the manufacturer of the study drug, as required, based on the study type		●
Performing of AE reconciliation, as required based on study type		●
Reporting of safety data to HAs, as appropriate		●
Analysis of study data, preparation of interim and final study reports and forwarding them to Novartis		●
Submitting draft publications to Novartis prior to submission to a scientific congress or journal		●
Independently publishing the clinical trial results		●
Reporting study results to HAs, if required according to local regulations		●

Abbreviations

ADR = Adverse Drug Reaction

AE = Adverse Event

EC = Ethics Committee

FMV = Fair Market Value

FPFV = First Patient First Visit

GCP = Good Clinical Practice

GEMS = Grants, External Studies, Managed Access System

HA = Health Authority

IIT = Investigator Initiated Trial/Study

IRB = Institutional Review Board

LPLV = Last Patient Last Visit

MSL = Medical Science Liaison

PK = Pharmacokinetic

SAE = Serious Adverse Event

SUSAR = Suspected Unexpected Serious Adverse Reaction

TPSR = Third Party Study Report

In addition to the requirements set forth in this guidance document, each request will be assessed subject to applicable local laws and regulations

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