Investigator's Brochure

The Investigator's Brochure (IB) is similar to prescribing information (or drug label), but for an investigational drug. It summarizes all of the known nonclinical and clinical safety and efficacy information of the drug; the intent is to inform clinicians of the potential toxicity of the drug. A key section of the IB defines the adverse events that are considered "expected" for the purposes of expedited safety reporting for the drug based on observations to date. The IB is updated at least annually for as long as the drug is undergoing clinical trials to ensure the information is current.

INDS AND CTAS: SIMILARITIES AND DIFFERENCES

Although the purpose of both INDs and CTAs is to enable studies of investigational drugs in people, the two types of submissions fulfill different requirements and are thus composed of overlapping yet nonidentical components.

In the United States, the initial IND includes multiple forms specific to the FDA, all nonclinical study reports (including validation reports of bioanalytical methods), nonclinical summaries (key information from the reports summarized concisely), detailed CMC information, as well as the protocol and IB (see Data to Support Initial Clinical Trials section above and 21 Code of Federal Regulations (CFR) 312.23).[19] Once an IND has been cleared by the FDA (see details below), multiple studies can be conducted under the same IND, as per the FDA's legal requirements, the CFRs (21 CFR 312.22).[19] These studies must use the same investigational drug and be used in patients with the same disease (i.e., the same indication), but after the initial clearance, subsequent protocols can be initiated immediately after submission to the IND without a waiting period (subject to approval by an IRB) and assuming appropriate supporting documents are available, such as nonclinical reports (21 CFR 312.30).[19] The majority of the IND, including the nonclinical and clinical summaries, is only submitted once as part of the initial IND. Subsequent new protocols submitted to the IND are considered *IND amendments*. Amendments are made to the IND throughout its lifecycle and also encompass submissions to update the drug product information and new nonclinical and clinical reports (see IND Maintenance section below).

Some research studies may not require the filing of an IND (see **Figure 1**).[20] For studies that require an IND, there are two IND categories: commercial and research INDs, differentiated by the entity that submits the IND and the purpose of the clinical research (see **Figure 1**). Commercial INDs are usually submitted by biopharmaceutical drug companies with the intent of eventually submitting a marketing application to sell the drug commercially. Research INDs are submitted by investigators to test a new dose or indication of an existing drug, but the data to be generated from the study are not intended to be used for a subsequent application for market approval.

For drugs that are in very early development, an abbreviated IND, called an exploratory IND, may be submitted to allow drug sponsors to evaluate up to five chemical entities or formulations simultaneously, supported by limited nonclinical data (see **Figure 1**).[21] Exploratory INDs provide the opportunity to study pharmacokinetic and target interaction early in drug development. When a lead candidate drug has been selected, the exploratory IND is closed, and a traditional IND is opened.

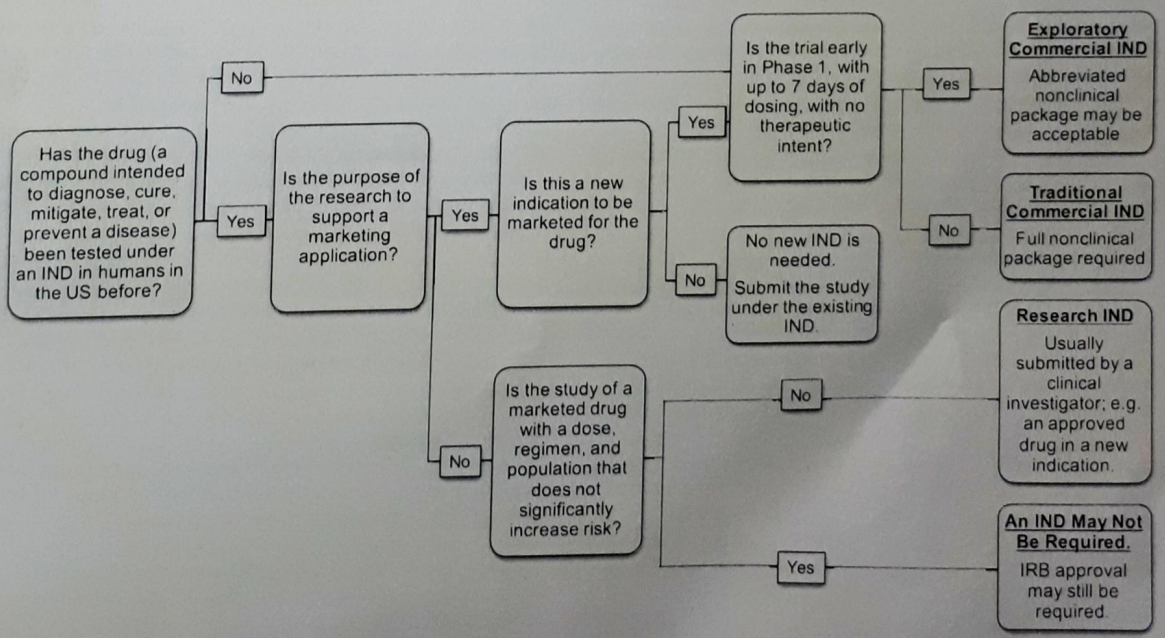

Figure 1 To (IND) or not to IND... IRB, instutional review board. Note: Exceptions are possible. Information summarized from refs. 20–22.

In the European Union, *each interventional clinical study* requires a new CTA.[22] Because of the different purposes of these submissions, the documentation required for a CTA is not identical to that for an IND. For a CTA, the four main documents are the protocol, informed consent form, IB, and Investigational Medicinal Product Dossier (IMPD), which contains CMC data. Additional information such as European Union–specific forms, questionnaires, or patient diaries to be used in the trial, and insurance certificates, must also be included.

LIFECYCLE OF AN IND AND CTA

IND initial clearance

INDs are not "approved"; they are "cleared." The FDA reviews initial INDs in 30 days (21 CFR 312.20).[19] An IND can be opened with a study of any phase (i.e., phase I, II, or III; 21 CFR 312.21).[19] Questions from the FDA that arise during the review of the IND are communicated to the Sponsor, usually during the last 2 weeks of the 30-day review. A teleconference may be needed to clarify these issues. The Sponsor then addresses the FDA's concerns by providing additional information and/or revising the IND documents as needed. If the FDA's concerns are adequately addressed such that they consider the study safe to proceed, the IND is cleared after 30 days. If, however, the FDA's concerns remain, they may place the IND on full or partial clinical hold (21 CFR 312.42).[19] A full hold means that no clinical study can be initiated under the IND until the FDA's issues are satisfactorily addressed. A partial hold means the clinical study and any other studies submitted under the IND may proceed with certain constraints (e.g., the investigational drug may not be administered above a certain dose). The Sponsor must then provide a complete response to the clinical hold, which also has a 30-day review period. The FDA may lift the hold if the response addresses the identified issues and clears the IND, thereby allowing studies under the IND to proceed, or the FDA may maintain the clinical hold. Because future protocols submitted under an IND are allowed to proceed without the review, the FDA may be cautious when clearing the initial IND. However, the FDA may place an IND on clinical hold if any concerns arise at any time during the lifecycle of the IND; this prerogative is not restricted to the first 30 days of the IND submission.

CTA initial approval

Review, approval, and maintenance of CTAs in the European Union are currently ruled by Directive 2001/20/EC, a nonbinding set of rules for the European Union Member States (MS: countries that are part of the European Union) to interpret and implement with a relative degree of freedom. In replacing this Directive with Clinical Trial Regulation (CTR) 536/2014,[8] which will go into effect in 2020, the European Commission aims to enhance the harmonization of the CTA process across MS for a more efficient and consistent supervision of clinical trials in the European Union.

The shift from Directive to Regulation is significant and will enable simultaneous submissions of HA and EC applications. Beyond the pure procedural changes, the new CTR will address other key issues, such as increased transparency and access and more efficient linkage to the EudraVigilance database for a more consolidated generation and monitoring of safety data. (EudraVigilance is the EMA's system for monitoring the safety of medicines by facilitating electronic reporting of suspected adverse reactions and enabling the early detection of potential safety issues.)

Current directive 2001/20/EC. The Directive is applicable to all MS, where national laws apply as well. This leads to variance in interpretation and local practice (e.g., between individual MS HAs and ECs), nuances of format and content, review timelines, and more.

The introduction of the Voluntary Harmonisation Procedure (VHP) in 2009 was the first attempt of better alignment between MS. The VHP enables a Sponsor to submit a CTA to multiple MS in parallel and perform a single combined scientific review. Although single-country national CTAs are still an available option, here, we will focus on VHP as a precursor to the upcoming CTR 536/2014.

The VHP procedure extends through three phases:

1. Request for VHP application and validation
2. Assessment by selected MS
3. Formal submission of the VHP-approved CTA to the local HAs

The average timelines for a national CTA is 60 days plus any additional time the Sponsor requires to respond to any questions from the HA, whereas the average time for CTAs via VHP from start to finish was 52.5 days, including time for the Sponsor to respond to questions (see **Figure 2**).[23,24]

New CTR 536/2014. There are multiple innovations and efficiencies with the new CTR. Besides enabling submissions through one gateway and using a single set of documents, the CTR permits concurrent and harmonized involvement of the ECs, which will still be governed by local rules but will need to adhere to the new procedure timelines. This will lead to more reliable and predictable review and approval timelines for the European Union CTAs.

CTR CTAs will be submitted based on a single dossier split in two modules, as shown in **Table 2**.

The two-part assessment leads to a single approval per member state, replacing separate approvals by the local HA and EC.

The timelines for review and approval are supported by tacit approval, holding the participating MS accountable for their timeline commitment. The timelines for CTA approval under the CTR are expected to be comparable to current VHP timelines.

IND maintenance

Once an IND is in effect, there are three primary maintenance activities and responsibilities for Sponsors: amendments, safety reporting, and annual reports.

Amendments. The IND is often amended throughout its lifecycle. There are two types of IND amendments: Protocol Amendments and Information Amendments.

Protocol amendments are to ensure that the clinical investigations are conducted according to the protocols included

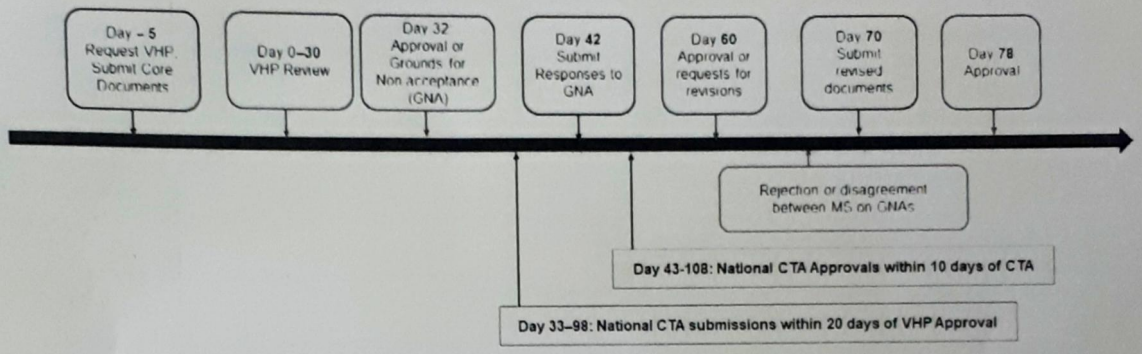

Figure 2 Standard Voluntary Harmonisation Procedure timelines. Average timelines for national clinical trial application (CTA) evaluation: 60 days + clock stop for questions. Average timeline for Voluntary Harmonisation Procedure (VHP): 52.5 days, including time for questions. Information summarized from refs. 23 and 24.

Table 2 Modules for the New Clinical Trial Regulation CTAs

Part 1: Study-specific Assessed by all participating member states	Part 2: – Country and site-specific Assessed by each member state separately
Application form	ICF
Protocol	Recruitment arrangements
IB	Rules of liability
IMPD	Suitability of investigators and trial sites
IMP manufacturing, labeling, and import	Financial compensation
Any HA advice received	Data protection requirements
PIP	

CTA, clinical trial application; HA, health authority; IB, Investigator's Brochure; ICF, informed consent form; IMP, investigational medicinal product; IMPD, Investigational Medicinal Product Dossier; PIP, pediatric investigational plan.

in the application (21 CFR 312.30).[19] Examples of protocol amendments include:

- New protocol: As discussed above, an IND may contain multiple studies of the same investigational drug in the same patient population or indication. A protocol for a new clinical trial may be submitted to an IND that has cleared (i.e., an open IND). New studies may begin soon after the protocol has been submitted to the FDA and has been approved by the IRB. The IND submission should include a copy of the new protocol and a brief description of the most clinically significant differences from previous protocols.
- Change in existing protocol: Sponsors must submit a protocol amendment to describe any changes in protocols that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study. A protocol change intended to eliminate an apparent safety hazard to subjects may be implemented immediately, provided that the FDA and the IRB are subsequently notified. The IND submission should include a brief description of the changes and a reference to the submission that contained the original protocol.
- New investigator: The FDA should be notified within 30 days of the addition of a new investigator to conduct a study previously submitted to the IND (21 CFR 312.23).[19] The submission should include the investigator's name, qualifications, reference to the previously submitted protocol, and other additional information.

Information amendments are any amendments to information essential to the investigational drug and can be categorized as relating to chemistry/microbiology, pharmacology/toxicology, clinical, statistics, or clinical pharmacology (21 CFR 312.31).[19] These are submitted to the FDA as necessary but generally no more frequently than every 30 days. The submission should include a statement of the nature and purpose of the amendment.

Safety reporting. Sponsors must notify HAs and all participating investigators of potential serious risks associated with the use of the investigational drug based on prompt review of all relevant safety information (21 CFR 312.32).[19] These include serious and unexpected suspected adverse reactions, findings from other studies, findings from animal or *in vitro* testing, or increased rate of occurrence of serious suspected adverse reactions. Each safety report, in narrative format, should be submitted as soon as possible but no later than 15 calendar days following the Sponsor's initial receipt of the information. Any unexpected fatal or life-threatening suspected adverse reaction reports should be reported as soon as possible but no later than 7 calendar days following the Sponsor's initial receipt of the information. If applicable, relevant follow-up information to an initial safety report must be submitted as a Follow-up Safety Report as well.

Annual reports. Sponsors are expected to submit a brief report of the progress of the studies conducted under their IND application annually within 60 days of the anniversary date that the IND went into effect (21 CFR 312.33).[19] This annual update and summary is intended to inform HAs of the progress of a drug's development program during the past year and identifies any potential issues or safety concerns in the program

Box 4 Annual report requirements

Individual study information: A brief summary of each study under the investigational new drug (IND), the status (ongoing or completed) of each study, summary of subject enrollment to date, and overview of available results.

Summary information: Summary of clinical and nonclinical investigations, including the most frequent and serious adverse events, IND safety reports submitted in the past year, any deaths, subject discontinuations due to safety, information pertinent to an understanding of the drug's actions (e.g., dose response, bioavailability, etc.), list of nonclinical studies and findings, and any significant manufacturing or microbiological changes.

General investigational plan: Brief description of the overall plan for investigating the drug product for the following year, including rationale for study(ies), indication(s), general approach, kinds of clinical trials to be conducted, estimated number of subjects, and any risks of particular severity or seriousness anticipated on the basis of toxicological data.

Investigator's Brochure updates.

Significant phase I protocol modifications not reported to the IND in a protocol amendment.

Brief summary of significant foreign marketing developments.

If desired, a log of any outstanding business with response to the IND for which the Sponsor requests or expects a reply, comment, or meeting.

(including a summary of any issues beyond routine safety reporting), see **Box 4**: Annual Report Requirements. The Sponsor may report this information as outlined in the inset or use the Development Safety Update Report format as outlined in ICH E2F[25] with prior approval from the FDA.

IND withdrawal and inactivation. A Sponsor can withdraw an effective IND at any time without prejudice (21 CFR 312.38).[19] The appropriate HAs should be notified, all investigations ended, all investigators notified, and all investigational drugs returned to the Sponsor or disposed of appropriately. If an IND is withdrawn for safety reasons, the Sponsor should inform the appropriate HAs, all investigators, and IRBs of the reason(s) for the withdrawal.

An IND can be placed on inactive status by the FDA or upon request by the Sponsor if no subjects are entered into clinical studies for 2 years or more, or if all investigations under an IND remain on clinical hold for 1 year or more (21 CFR 312.45).[19] As with an IND withdrawal, all investigators should be notified and all drugs should be returned to the Sponsor or disposed of appropriately. An IND Annual Report is not required to be submitted to an IND on inactive status. The IND may be reactivated by submitting an amendment containing the proposed general investigational plan for the coming year and appropriate protocol(s). If an IND is on inactive status for 5 years or more, it can be terminated by the FDA.

CTA maintenance

Many of the same aspects of IND maintenance are applicable to CTAs as well.

- Protocol amendments: Substantial changes to the protocol must be approved by the relevant HA and EC prior to implementation, unless changes are required to immediately protect the safety of study subjects.
- Safety reporting: Safety reporting requirements are similar to those in the United States. Safety data in the European Union are reported via the EudraVigilance system.
- Annual reports: Annual reporting to the EMA is typically in Development Safety Update Report format.

In addition, changes to the CMC information are submitted to the relevant HAs as an amendment to the IMPD.

CTA end-of-study notification. After the official end of a clinical study, as defined in the protocol, typically the last visit by the last subject enrolled in the study, Sponsors are required to notify the relevant HAs and ECs that a clinical trial has concluded.

INDS VS. CTAS: SUMMARY

Above, we have outlined the process and requirements for initiating clinical trials with an investigational drug in the United States and the European Union. Although both INDs and CTAs require the same basic data set to support initiation of clinical trials in humans, the documentation required for HA review and the process for application review and approval differs considerably between the two. CTAs contain fewer documents than INDs, requiring less preparation time. INDs have well-defined timelines to clearance (30 days); in contrast, there can be considerable variability in the approval process between each MS's HA and EC (e.g., parallel vs. sequential review, set or limited submission times, variable review lengths, etc.). With INDs, there is no cost or time delay to amend or add new protocols (assuming sufficient nonclinical and CMC information are already present in the IND), whereas substantial protocol amendments require CTA approval, and new protocols require new/separate CTAs. CTAs do not carry potential risk for clinical hold like INDs do; the CTA is either approved (perhaps with mandatory changes) or rejected.

CONCLUSION

Sponsors are required to consolidate data from CMC, pharmacology, pharmacokinetics, nonclinical toxicology, and clinical development into a cohesive plan to evaluate the potential safety and efficacy of a potential new drug in humans, while taking every necessary precaution to protect clinical study subject safety. Whether provided in an IND or

CTA, the data required to support the initiation of a clinical trial of a new drug in humans are justifiably substantial, and significant time and resources are required to enable a successful submission and approval.

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