The Investigator’s Brochure: An Insider's Insight

Considered a multidisciplinary document, the Investigator’s Brochure provides a summary of research work completed on an investigational medicinal product. It serves several purposes and evolves as the development program progresses. Some Sponsors see the Investigator’s Brochure as a virtual ‘history’ of a programme itself.

Here we give a view of what your Investigator’s Brochure should look like derived from experience gained over Niche’s 20 years in the business. The information provided here complements our freely available Investigator’s Brochure document template [1]. With over 900 downloads, the template is the most accessed document on The Niche Science & Technology Ltd. website.

Before you start

The information in a well prepared Investigator's Brochure is highly accessible.

As the development of a drug progresses details about early development such as pre-clinical methods can be reduced

Brochure text should not be promotional nor draw generalised conclusions about efficacy

Plan for a 80 – 100 page document with internal cross links between section and data sources

Prepare to succeed

List the details of studies in tables at the front of sections

Referencing the scientific literature aids with brevity

Be concise. In-text tables and figures can be an effective means of reducing text and summarising findings

Don't prepare the summary at the front of the Investigator's Brochure until the main body of the text has been finalised and approved

Key Insights

The Investigator's Brochure is an axis document in a new drug's clinical development programme. Crucial to various processes that regulate clinical research into new drugs, its content is well defined. The ICH E6 guideline specifies that an Investigator's Brochure should include information on the drug product to be investigated and its performance in non-clinical studies along with specific guidance to investigators on the drugs use. By its very nature the Investigator's Brochure is a multidisciplinary document, summarising information from each of the teams involved in a drug's development.

When considering the information to report in your Investigator's Brochure it is crucial to remember its purpose:

> To provide information to the Investigator and others involved in a clinical study on such issues the appropriateness of dose, dose frequency/interval and the characteristics of the investigational medicinal product (IMP) – so that it can inform safety considerations and clinical management of study subjects during a clinical trial.

The document should be concise (in practice an Investigator's Brochure should not exceed about 100 pages), clear and focused while remaining balanced and sufficiently complete to communicate what an investigator needs to know about using the IMP. As well as serving as the primary reference document for determining whether an adverse event is 'unexpected' (for purposes of reporting to regulatory authorities), the Investigator's Brochure plays other roles:

- A regulatory prerequisite for clinical studies, as specified in the ICH E6 Guideline for Good Clinical Practice [2]
- Consideration by independent ethics committees
- A requirement for Investigational New Drug applications (USA)
- To support Investigational Medicinal Product Dossier and Paediatric Investigation Plan submissions in Europe
- To form the basis of other documents – briefing packages and summaries required for marketing authorisation

Unspoken

There is an 'unspoken' function for Investigator's Brochures. Research on many new treatments is initiated in small start-up and biotech companies. These companies often base their business model on venture capital investment and (eventually) sell their assets to larger pharmaceutical companies, who will take a product through to commercialisation. In both these situations the Investigator's Brochure is used as a showcase for a new product. The Investigator's Brochure should not be promotional nor draw generalised conclusions about efficacy.

Structure and 'front end'

The front of an Investigator's Brochure contains housekeeping information. It includes the Sponsor's details, identity of the investigational product(s), any research identification codes, the product's chemical or approved generic name, tradename(s) and the document's version and release date. Some Sponsors also like to include a statement instructing the Investigator/recipient to treat the Investigator's Brochure as a confidential document.

Complex terms used within the document and abbreviated within the text are summarised in a list (most often at the front of the Investigator's Brochure).

The structure of an Investigator's Brochure structure is defined within ICH E6 (Section 7) [2]:

- Summary
- Introduction
- Physical, chemical, and pharmaceutical properties and formulation
- Non-clinical studies
- Effects in humans
- Summary of data and guidance for the Investigator

Summary

The secret of a well-prepared Investigator's Brochure is accessibility of its information. To aid this, a summary of the content is provided at the front of the document.

The summary should provide a high-level overview of the documents content, presenting a profile of physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information. The Summary should 'preferably' not exceed two pages (ICH E6) [2] – although this becomes more difficult to achieve as the development programme for an IMP progresses and the amount of data to report and summarise increases.

Hint: When writing a new Investigator's Brochure or updating a previous version, it is generally advised that you should not attempt writing/updating the summary until the main body of the document has been finalised and approved. This will guard against discrepancies between the content of the Investigator's Brochure and the summary being introduced as new versions of a document are produced.

Introduction

The Introduction should be 1–2 pages in length and provide a high-level overview of the IMP and the setting of its proposed use. The introduction should provide a background on the therapeutic rationale behind an IMPs use and its target indication. It should include the generic name and the tradename of any drug product, its active ingredient(s) and the pharmacological class along with a summary of its position within this class. The content should reference the scientific literature and incorporate aspects of the IMPs clinical development plan and associated briefing packages.

"The ability to simplify means to eliminate the unnecessary so that the necessary may speak."

Hans Hoffmann

The introduction should include any anticipated prophylactic, therapeutic and/or diagnostic benefits as well as potential risks. Some sponsors like to include a cut-off date for information incorporated in this version of the document and a brief statement on the product's stage of development and/or licensing status.

Physical, chemical, and pharmaceutical properties and formulation

Often called the 'CMC section' by old-timers (standing for Chemistry, Manufacturing and Controls) the text is intended to provide a brief description of the chemical, physical and pharmacological properties of the active ingredients or drug product (active ingredient) and, where relevant, a quantitative statement of active ingredient for each dosage form of the drug substance. It should include:

- Product code names, information relating to the chemical structure and physical form/solubility of the drug substance relevant to clinical use/formulation.
- Qualitative list of all excipients without excipient grades and justification for inclusion of the excipients in the formulation if clinically relevant.
- Details of any matching placebos if relevant.
- Recommendations on storage and handling of the dosage form. This may be by reference to the product label.

Substance versus Product

The term drug substance describes an active ingredient that is intended to furnish pharmacological activity or other direct effect. In contrast, drug product relates to a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Non-clinical studies

The structure of this complex section is described within ICH E6 [2]. It should report on all relevant non-clinical pharmacology, toxicology, pharmacokinetic and investigational product metabolism studies, reporting on the nature and frequency of effects. In addition to summarising the time of onset and duration of any effects and any dose response findings the reports should summarise information on:

- Species tested
- Number of sex in each group
- Unit dose (e.g., mg/kg)
- Dosing intervals
- Route of administration
- Duration of dosing

Referencing the scientific literature can aid brevity when describing the use of standard methodology while the strategic use of tables and figures can be a good way of summarising study findings.

The non-clinical data is reported in specific sections detailed below. Early pre-clinical studies characterising an IMPs profile tend to be conducted under 'experimental' conditions whereas drug toxicity, genotoxicity and safety pharmacology need to be conducted under Good Laboratory Practice (GLP) conditions. You should report whether or not a study was conducted under GLP conditions.

Non-clinical test material

Experiments conducted in the early stages of development may be conducted with an IMP prepared using different methods than those used to produce clinical batches. This can have relevance to observations and therefore should be summarised. Information might include the impurity profile and how it compares to the profile of the material proposed for use in clinical investigations. A description of how dosages are expressed should also be provided, i.e., in terms of free form base or acid or in terms of salt etc.

Non-clinical studies (cont.)

Non-clinical pharmacology

During the process of development a broad variety of experiments are conducted in a variety of *in vivo* and *in vitro* settings. They tend to be identified as primary, secondary or safety pharmacology studies. Primary studies relate to the targeted actions of the product and secondary studies usually provide involve efforts to characterise the general pharmacodynamic profile beyond the IMPSs primary indication. Safety pharmacology report studies that provide data that may be relevant later in development in terms of potential safety implications. Studies should be reported in a hierarchical fashion (primary, secondary, safety) with *in vitro* studies reported before *in vivo* studies. A table is often used to summarise the types of studies being reported (Example 1).

Example 1

A range of *in vitro* and *in vivo* studies were conducted to investigate the primary and secondary pharmacology of NST001. In addition, safety pharmacology studies have been conducted in rats and dogs. A listing of these studies is provided in Table 1.

Table 1. Studies investigating the pharmacology of NST001

Phase	Type of Study
Primary Pharmacology:	In vitro binding affinity
	Gerbil foot tapping model
	Anti-emetic activity in shrews and ferrets
	Marmoset human threat test
Secondary Pharmacology:	Receptogram screen
Safety Pharmacology:	Overt central and peripheral pharmacodynamic effects in Han Wistar rats
	Overt central and peripheral pharmacodynamic effects in beagle dogs
	Cardiovascular, electrocardiographic and respiratory effects in Han Wistar rats
	Cardiovascular effects in beagle dogs (oral administration)
	Cardiovascular effects in beagle dogs (iv administration)
	Dog Purkinje fibre assay

During early development, study summaries should contain details on the methods used, the study findings and a conclusion on the relevance of any findings relative to the proposed effects. As development progresses, details on the materials and methods can be condensed and results put in context with any reported findings in humans. For example, if there are human studies showing blood pressure lowering effect of an antihypertensive drug, it is no longer necessary to show data-rich tables and/or graphs of blood pressure lowering effects in animals. A statement to the effect that the blood pressure lowering (possibly with an average lowering effect) observed in the spontaneously hypertensive rat was predictive of the blood pressure lowering effect observed in humans (referring to where the data is reported in Investigator's Brochure).

As a product enters the later stages of development a brief (1 – 3 pages) summary of the key non-clinical findings may be sufficient. At this stage, the nonclinical pharmacology section should summarise the pharmacologic activity substantiated in humans and a table of the key findings will often suffice.

Non-clinical studies (cont.)

Pharmacokinetics and product metabolism in animals

Describe succinctly the analytical methods used to measure IMP levels in blood, urine and tissue, outlining assay validation.

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be reported. The start of this section often summarises the types of studies that have been conducted in tabular format as detailed in Example 2. As development progresses, details on the materials and methods can be condensed and results put in context with the reported findings in humans.

Example 2

The pharmacokinetics, distribution, metabolism and elimination of NST001 have been investigated through a series of oral, intravenous and in vitro studies in the rat, dog and monkey using unlabelled and [^{14}C]-labelled drug. A list of the studies conducted is provided in Table 2.

Table 2. Pharmacokinetic and metabolism studies conducted with NST001

Type of Study	Dose Route	Salt Form	Dose (mg/kg) or Concentration	Species	No. /Group
Toxicokinetics: 14-day study	Oral	B	10, 50, 300	Mouse	3M
Toxicokinetics: 13-week study	Oral	B	25, 50, 100	Mouse	3M/3F
Pharmacokinetics	Oral	A	5	Rat	5M
	iv		2		3M
Toxicokinetics: 14- and 21-day studies	Oral	B	3–80	Rabbit	3–4F
Pharmacokinetics	Oral	A	5	Dog	3F
	iv		2		3F
Toxicokinetics: 4- and 13-week studies	Oral	B	0.5–30	Dog	3–9M/ 3-9F
Pharmacokinetics	Oral	A	3	Monkey	2M/2F
	iv		1		2M/2F
Permeability	*In vitro*	B	0.5–200 µM	NA	NA
Tissue distribution	Oral	G	5	Rat	1–3M
Red blood cell association	Oral	G	10	Mice	3M/3F
	Oral	G	5	Rat	3M/3F
	iv	G	1	Rat	6M
	Oral	G	3	Dog	3M/3F
	Oral	G	3	Rabbit	4F
Metabolism	*In vitro*	F, B	0.5–50 µM	Rat, Human	NA
Cytochrome P450 enzyme induction	*In vitro*	A	0.5–25 µM	Rat	NA
Metabolite profiling	Oral	G	10	Mouse	3M/3F
		B	50–600	Rat	d
		G	3	Rabbit	4F
		B	3, 10–50	Dog	3M/3F
Elimination	iv	G	1	Rat	6M
(intact and bile duct cannulated)	Oral	G	5	Rat	3M/3F
	Oral	G	3	Dog	3M/3F
	Oral	G	3	Rabbit	4F

M = Male; F = Female

Toxicokinetic studies provide a critical evaluation of drug disposition at toxicologic doses while investigating relationships between drug levels and the occurrence and time course of toxic effects. With objectives different from pharmacological challenges in such factors such as solubility, stability, absorption etc. that are affected by the dose size [3].

Non-clinical studies (cont.)

Pharmacokinetics and product metabolism in animals (cont.)

Focus	Content
Distribution	Information from whole body autoradiography studies should be presented along with observation from in vitro protein binding (all species including human) and any milk and placental transfer studies.
Metabolism	Metabolic profiling and identification should be provided for all toxicological species together with in vitro data from multispecies microsomes, hepatocytes or liver slices.
Balance Excretion	Quantitative information on the amount of drug-related material excreted in urine, faeces, expired air and/or remaining in the carcass should be provided together with any data generated in bile-cannulated animals.
Interactions	Information on potential pharmacokinetic drug interactions should be provided. Normally, data generated in in vitro studies using human microsomes and in vivo studies looking at enzyme induction (generally derived from the 1-month toxicological investigations) would be included and other relevant data such as protein binding or renal excretion may also be discussed on a case-by-case basis.
Other Studies	This section is included when needed to cover information from special studies performed to investigate effects specific to the IMP and/or its administration.

During the early stages of development summaries are expected to contain details on the methods used, the results and relevance of any findings to the proposed effects. The discussion of the findings for this section should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

Toxicology

As with the section on pharmacokinetics, data on the types of studies conducted should be provided in tabular format including details on the animals studied and dose (see Example 3). Information provided follows a hierarchical structure: single dose, repeated dose, carcinogenicity, special studies (irritancy, sensitisation etc.), reproductive toxicology and genotoxicity (mutagenicity) studies. Data on in vitro and in vivo studies conducted in mammalian and non-mammalian species should be presented separately

Study summaries should describe the rationale and results as well as commenting on the relevance of the findings to the proposed clinical usage and discuss exposure cover at toxicological no-effect dosages. Where reproductive toxicity studies have been conducted effects on fertility, reproductive performance, foetal organogenesis, and peri- and post-natal development should be discussed. Special studies might involve assessment of irritancy and sensitisation tests and studies done to evaluate haemolytic potential for intravascular study drugs.

This section may include cross-references to the section providing guidance to the investigator, where an integrated discussion of the non-clinical data will be provided including discussion of its relevance to the use of the study drug in human subjects (emphasising the key safety issues).

Non-clinical studies (cont.)

Toxicology (cont.)

Example 2

Single and repeat administration studies have been conducted in mice, rats, dogs and monkeys. Fertility and embryofoetal development studies have been conducted in rats and rabbits. Local tolerability (intravenous) studies in dogs and *in vitro* haemolysis evaluations have also been conducted. A battery of *in vitro* and in vivo genetic toxicity studies were also performed. A listing of studies conducted is presented in Table 3.

Table 3 Toxicology Studies Conducted with NST001

Study Type/ Duration	Dose Route	Salt Form	Dose (mg/kg) or Concentration	Species	No. /Group
Single Dose					
Acute toxicity	Oral	B	1000-1500	Mouse	2-7M/0-6F
Repeat Dose					
14 day	Oral	B	10, 50, 300	Mouse	6M/6F
13 weeks	Oral	B	25, 50, 100	Mouse	12M/12F
31 days	Oral	B	5, 15, 50	Rat	12M/12F
4 weeks	Oral	B	1.5, 20	Dog	3M/3F
13 weeks	Oral (tablet)	B	1, 3, 10	Dog	3M/3F
3 months	Oral	B	2.5, 10	Monkey	3M/3F
4 day	iv	B	2.5, 5, 10	Rat	4M/4F
Reproductive Toxicity					
Fertility	Oral	B	5, 15, 50	Rat	24M/24F
Embryofoetal development	Oral	B	5, 15, 50	Rat	30F
Genotoxicity					
Ames assay	*In vitro*	B	0.1 - 2500 µg/plate	NA	NA
Micronucleus test	Oral	B	150, 300, 600	Rat	7M
Special Toxicology					
Haemolysis	*In vitro*	B	0.17 mg/mL	Dog, Human	NA
Local tolerability	iv	B	10 mg/dog	Dog	3M
4-week investigative	Oral	B	5, 50	Rat	10M/10F
12-day investigative	Oral	B	50	Rat	6M

NA: not applicable.

Non-clinical assessment of safety

This important section serves to interpret the findings of the non-clinical programme in the form of a brief description (1-2 pages) of the scope of the work conducted and the extent to which the IMP has been shown not to cause abnormalities and/or toxicities.

A summary is also provided on observations that could be considered adverse findings, non-adverse toxicological findings and findings of unknown significance. Levels of exposure to the IMP and no adverse event levels are also provided along with effect reversibility and possible clinical significance. This section usually includes an estimate of the levels of exposure (in terms of dose and time) that would be considered acceptable in humans.

Key terms

The no-observed-adverse-effect-level (NOAEL) is an important part of the non-clinical risk assessment. It is a professional opinion based on the design of the study, indication of the drug, expected pharmacology and spectrum of off-target effects. There is no consistent standard definition of NOAEL. It is based, in part, on the varied definitions of what constitutes an adverse effect. Toxicologists, either investigating or reviewing, have not been consistent in defining an effect as either adverse or acceptable. The common definition of NOAEL, 'the highest experimental point that is without adverse effect,' serves us well in general discussions. It does not, however, address the interpretation of risk based on toxicologically relevant effects, nor does it consider the progression of effect with respect to duration and/or dose [4].

The maximum tolerated dose (MTD), also known as the maximum tolerable dose or maximally tolerated dose, is defined as the dose that produces an 'acceptable' level of toxicity or a dose that, if exceeded, would put animals (or patients) at 'unacceptable' risk for toxicity [5].

Effects in Humans

If the Investigator's Brochure is intended to support a first-time-in-human study and no clinical studies have yet been conducted this section should be left blank.

Introduction

Where clinical studies have been conducted this section should start by noting the stage of development for the IMP and summarise the studies that have been conducted. A description of each completed clinical trial should be provided; ICH E6 states available information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities should be included [2].

As recommended for the non-clinical studies, a table of the investigational studies performed to date is desirable (see Example 4). The summary may also provide data on doses used and a total for the number of subjects included in clinical studies as well as information on which studies were conducted in healthy volunteers and which patients. In Investigator's Brochures intended for early phase investigations data should only be included on studies that have been formerly reported.

Example 4

Table 4. Clinical studies performed (Clinical cutoff – 12 Dec 2007)

Study Design	Population	Doses	Main Result
Single dose, rising dose	16 M volunteers	1 to 100 mg	Well tolerated; QT prolongation at 25 mg
Repeat dose, rising dose	24 M volunteers	25, 50, 75 and 100 mg bid x 7 days	Well tolerated; dose related prolongation of QT
PK in the elderly volunteers	12 M/F 24-40 yo 12 M/F 65-80 yo	100 mg bid x7 days	No difference in tolerability
PK in renally impaired	12 M/F >18 yo	acutely and then 100 mg bid x7 days	No change in GFR or RBF
Effect of food	16 M volunteers	100 mg	No effect

Key: M = male; F = female; PK = pharmacokinetics; GFR = glomerular filtration rate, QT = electrocardiogram time interval between the Q and T waves

This sections introduction may include statements about frequently observed adverse events, changes (or lack of) in ECGs, vital signs or laboratory values and general statements regarding any safety consensus that may not be covered elsewhere.

Brochures written in early development, when only one or two clinical studies have been reported, it is possible to report the clinical data by each study. However, once data from more studies become available they should be reported according to specific sections: pharmacokinetics and metabolism, safety and pharmacodynamics/efficacy.

Information on early phase studies becomes less relevant as development progresses. As focus switches to observations in patients, data on healthy volunteers becomes less relevant and can simply be reported in a brief (separate) textual summary. As development progresses further content may change again; as patient data increases with large Phase III trials it may be advisable to adopt a more inclusive approach to data from on going studies. When adopting this approach the writer should first provide information on observations in completed studies and then (blinded) data from on going studies.

Effects in Humans (cont.)

Pharmacokinetics and metabolism in humans

Observations in healthy subjects and patients should be reported separately. In both cases, a synthesis of information from single and multiple dose studies should provide a summary of the pharmacokinetic profile (including information on absorption, plasma protein binding, metabolism, distribution and elimination) and bioavailability (where available). This sections content is dictated by the IMP's stage of development. Information may be given on specific subject subgroups – typically by sex, age and hepatic and renal impairment. Additional aspects of disposition may include potential effects of other drugs and food on the IMPs pharmacokinetic profile and its potential effects on other drugs. Relevant subheadings can be added as appropriate to guide navigation.

Safety

This section should include the extent of exposure detailing the number of subjects included in the studies, active doses investigated and the number receiving placebo. In summarising safety observations, it is recommended to contextualise observations in terms of the study population by providing information on the demography of the subjects (age, gender, ethnicity) and their health, identifying healthy subjects of early phase investigations and the target disease population. It is also recommended that information is provided on the extent of exposure (doses used).

In early development (Phase I), it is beneficial to combine healthy volunteer data with clear indication of single and multiple dose exposures. This may not always be possible and the writer may want to consider how similar of study populations. It should be noted that data from drug-drug interaction studies should be presented separately as the potential for interaction creates its own unique safety considerations.

Suggested safety data subheadings are: single-dose studies, repeat-dose studies and drug-drug interaction studies. Each section should include information on the most frequently experienced adverse events along with a summary of the incidence of events and how they relate to IMP exposure. Serious adverse events should be clearly described along with any data implying effects on vital signs, ECG and/or laboratory measures. In some cases it is appropriate to provide information on individual subjects with emphasis placed on describing how any issue was resolved.

Pharmacodynamics and efficacy

In early phase development, focus is often placed on a pharmacodynamic marker intended to indicate the clinical potential of a new drug in its target disease. For example, a study may include 24 hour blood pressure monitoring when assessing a new treatment for hypertension. Investigator's Brochures written for Phase I/ II studies may have their own section reporting the IMPs pharmacodynamics effects. However, as an IMP enters Phase III, and investigations begin to determine clinical efficacy (in our current example that might be the ability of an IMP to lower blood pressure below threshold values). At this point pharmacodynamic data may be combined with that pharmacokinetics or be omitted.

When reporting the efficacy findings it is often difficult to pool the observations due to differences in study design. However, an attempt should be made to summarise efficacy findings across the range of studies and potential safety signals.

Marketing experience

Information should be provided on countries where the IMP has been marketed or approved and provide information of any relevant history of use and, if possible, an estimate of patient exposure. Countries where the investigational product failed to achieve marketing approval/registration or was withdrawn should also be recorded. Any post-marketing safety information available to the sponsor will also need to be summarized along with information from any pharmacovigilance databases. When the product is not marketed this section is left blank with a statement that the product is not yet marketed.

Summary of data and guidance for the investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data along with an assessment of the implications of the information.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials. Review and interpretation of the non-clinical and clinical experience is done so that inferences for the use of the investigational product in future studies can be drawn.

Practical information is provided for the management of subjects being treated with the investigational product. Information may also be drawn from published knowledge on other drugs in the same class. The information should be provided with clearly labelled subheadings, which often include: 'Therapeutic indications', 'Contraindications' and 'Warnings and precautions for use'. Possible subheadings are provided in the our Investigator's Brochure document template [1].

IMPORTANT

The main purpose of this section is to provide the investigator with a clear and readily accessible understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial.

It is expected that this understanding is based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s).

Guidance should also be provided to the clinical investigator on the identification and treatment of possible overdose and adverse drug reactions, guidance that is based on previous human experience and on the pharmacology of the investigational product. For Investigator's Brochures where there has not been any human exposure it should be stated that no data are available on the relationship of AEs to administration of the IMP, because no studies have yet been conducted in human subjects. For IMPs in early phase development it should be stated that limited data are available on the relationship of AEs to administration of the IMP because clinical experience is limited. In this case, state that the guidance for the investigator is based on nonclinical data and on the results of any Phase I/II studies.

References, Supplements and Appendices

There will be various instances where the text refers to the scientific literature. A Sponsor template will most likely have a standard style for citing the literature and how they are referenced. References may be provided at the end of each section of the document or be given in a combined list at the end of the Investigator's Brochure. References should not be made to Sponsor documents (as these may not be readily available to an investigator).

The Investigator's Brochure tends to be updated annually. However, during the early stages of development studies can be completed and reported in weeks or months, generating significant new safety data. This information may be provided in the form of a supplement. A supplement should be considered as a separate, standalone document and not a revision or an appendix. A supplement should adopt the format of the parent Investigator's Brochure. Information provided in a supplement should be fully incorporated into the next revision of the Investigator's Brochure.

Appendices should be provided where additional information to support that summarised in the body of the document could be helpful. For example, appendices might include description of key efficacy measurements, lists of additional clinical studies or lengthy adverse event tables.

An interview with our Head of Medical Writing

Q What is so different about writing an Investigator's Brochure?

A When you are working on an Investigator's Brochure you need to be a talented project manager and politician. You must gather input from representatives involved in every aspect of the drug development process. You need to manage each of their 'requirements' while ensuring that the document remains fit-for-purpose

Q What is the main challenge when writing an Investigator's Brochure?

A To ensure that the information presented in the document is as accessible and concise as possible and its focus is relevant to the IMP's stage of development, while remaining balanced and sufficiently complete in terms of the information that the investigator could possibly need to know. For this reason I would always suggest it is only attempted by an appropriately trained writer.

Q What is your #1 tip for working on an Investigator's Brochure?

A I would say that it is to remember that it is a living document and it changes with each iteration – changes can be minor in some cases but they are often significant. I would advise a writer to be aware of this and rather than thinking what can be added with each new revision they should be thinking what could be taken out.

Q You clearly enjoy working on Investigator's Brochures – why?

A The Investigator's Brochure offers a unique set of opportunities. First, you get to work with a broad range of scientists. Second, you get to learn about every aspect of an IMPs development. Finally, you get to practice a host of skills – medical writing, project and people management and how to interpret pharmacokinetic, toxicology and pharmacology data.

And finally…

It is worth repeating that the Investigator's Brochure is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. The information provided here should complement the Investigator's Brochure template provided on the Niche Science & Technology website [1]. Together our guides delineate the minimum information that should be included in an Investigator's Brochure and provide useful suggestions for its layout. However, little information is provided here on the process of development – a skill of its own – some excellent guidance is provided by Freberg [6].

We repeat also that the document is intended to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. Although it is often used as a promotional document for an IMP it is really intended to provide insight to support the clinical management of the study subjects during the course of the clinical trial. Thus, the information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make their own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason sponsors should resist turning it into an encyclopaedia.

Considering the important safety function this document provides it is highly recommended that a medically qualified person and trial-experienced team member participate in the preparation of the text and that individual sections be approved by the disciplines responsible for providing the data that are described.

References

1. Investigator's Brochure template www.niche.org.uk/asset/Investigator's%20Brochure%20Template.doc [accessed 10 December 2017].
2. International Conference on Harmonisation Guideline for Good Clinical Practice E6(R1) [cited Jun 1996]. Available from: http://www.ich.org/fileadmin/ Public_Web_Site/ICH_Products/Guidelines/Efficacy/ E6_R1/Step4/E6_R1__Guideline.pdf.
3. Welling PG, Differences between pharmacokinetics and toxicokinetics. Toxicol Pathol 1995:23; 143-7
4. Dorato MA, Engelhardt JA. The no-observed-adverse-effect-level in drug safety evaluations: use, issues, and definition(s). Regul Toxicol Pharmacol. 2005;42:265-74.
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Next Steps

We created this Insider's Insight to provide a few key learnings and share some helpful pointers we have acquired over the years. We hope you found it useful. We also point you to our ICH-compliant template, which is a great start to writing your own Investigator's Brochure. However, it is a complex and important document and for that reason I would always suggest it is only attempted by an appropriately trained writer.

If you would like advice on your own Investigator's Brochure challenge you can contact me at the email address below. We also run training sessions on how to write Investigator's Brochures from time to time, so please contact me if you would like to know when we will next be running one of these ever-popular training courses.

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