What you Need and When – The Key Documents in the Drug Lifecycle

Clinical development is a complex and expensive undertaking, involving many years of research that culminate with clinical trials, the objectives and results of which all have to be documented. This article provides a pathfinder to which documents need to be prepared, when they are needed, and who they need to be submitted to.

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Throughout the lifecycle of a medicine, documents are the key means for designing, conducting and reporting trials in human subjects, as well as for monitoring the quality manufacturing, packaging, labelling, safe usage and performance of drugs once on the market (see Figure 1). The ICH guidelines – particularly ICH E6 – provide a unified standard for the EU, Japan and the US to facilitate the mutual acceptance of clinical data by regulators within these jurisdictions, laying out the essential documents required to proceed through the clinical lifecycle and meet regulatory requirements (1).

Many of the documents needed are relatively straightforward forms that need to be completed with the appropriate information. Some, however, are more complex and require the efforts of multifunctional teams to pull together the information needed. In particular, experienced medical writers bring value to the process of weaving it all together in a way that effectively communicates the intentions and objectives of each document. This article aims to provide an overall summary of the documents that medical writers can, and should be involved in, as expert communicators who can ensure the documents are fit for purpose across the lifecycle of clinical drug development, approval and marketing. It will focus on the key documents required at each stage of the drug lifecycle, describing their content, purpose, audience, and deadlines for submission.

Documents Required Before the Start of a Clinical Trial

Prior to testing any new medicine or therapy on human subjects in a clinical trial, the drug developers must apply for permission to run clinical studies by submitting an Investigational New Drug (IND) application in the US or an Investigational Medicinal Product Dossier (IMPD) in any of the EU Member States (see Figure 1). For the initial human studies, these applications summarise manufacturing information, all

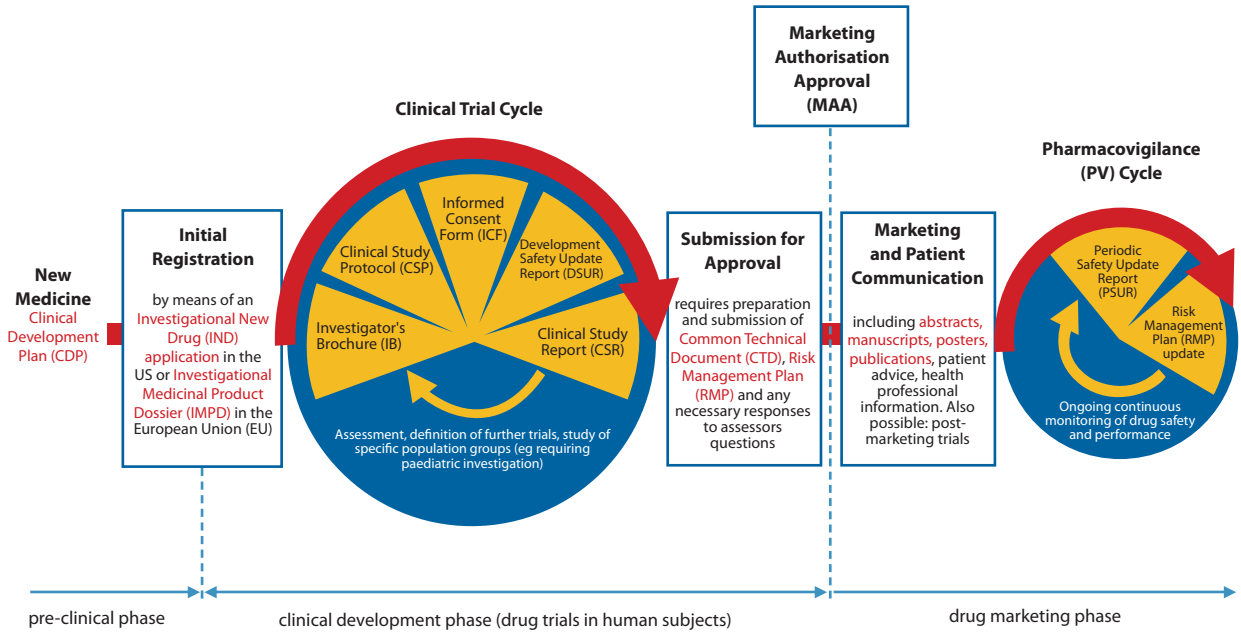

Figure 1: Documents in the drug lifecycle

EU documents	US documents	Nature and purpose
Investigational Medicinal Product Dossier (IMPD)	Investigational New Drug (IND) Application	An application for permission to use an investigational product in a clinical trial with human subjects. A separate IND or IMPD is required for each product used in a trial (including placebo). These documents may need updating for the approval of each new clinical trial, if the known information about an investigational product changes significantly
Investigator's Brochure (IB)	Investigator's Brochure (IB)	A compilation of all the relevant clinical and medicinal data of an investigational new drug or medicinal product, as relevant when studying the medicine in human subjects
Clinical Study Protocol (CSP)	Clinical Study Protocol (CSP)	A document that lays out strict guidelines for the performance of a clinical trial. Based on the most current data about the disease under treatment and the medicine being tested, the protocol lays out guidelines for diagnosis, prognosis, handling of subjects, dosage of medicines and risk/benefit considerations, providing decision options and their expected outcomes
Informed Consent Form (ICF)	Informed Consent Form (ICF)	A document to be signed by all subjects who are to take part in the clinical trial – to confirm that they understand and accept the objectives, methods and risks involved
Paediatric Investigation Plan (PIP)	Pediatric Study Plan (PSP)	A development plan that is required if the investigational product is to be licensed for use in children. It describes how clinical data will be obtained safely in clinical studies with children

Table 1: Documents needed to start a clinical trial

data available to date from animal studies including toxicity data, the clinical study protocols (CSPs) for the planned clinical studies and information about the investigators who will run the studies. As the development programme proceeds, the IND or the IMPD must be updated for each new study, adding new data from animal and human research available at the time the new study application is made.

There are a number of key documents that need to be written to be able to run the clinical studies, as explained in detail in ICH E6. The most important of the documents defined by ICH E6 are the CSPs, the informed consent forms (ICFs) and Investigator Brochures (IBs) (see Table 1 and Figure 1). The purpose of these is to:

- Lay out clearly the scientific information available about the product (in the IB)
- Explain the rationale for performing each study (in the CSP)
- Provide a detailed investigational plan and describe the analyses to be made to achieve the objectives of a study (in the CSP)
- Explain the details and intention of the trial in lay language for subjects participating in the trial (in the ICF)

These documents are often complex collections of thoughts that need to build on each other to tell a clear story of what the trial hopes to achieve and how. The coordination and writing of these documents warrants the use of an experienced writer who knows how to pull together input from the many stakeholders involved in the authoring process, and to make sure their ideas are consolidated into a consistent reflection of the planned studies.

It should be kept in mind that the complexity of these documents tends to increase as the development programme proceeds. Clinical development begins with Phase 1 clinical trials that are conducted with just a few human subjects to assess the safety and pharmacokinetics of the medicine. Phase 2 clinical trials follow, in which initial efficacy assessments are made in subjects with the target disease and dose finding studies are made to identify the optimal dosage of the medicine. Ultimately, large-scale Phase 3 trials are performed to unequivocally demonstrate the efficacy of the product at the planned dosage and to better understand the safety profile.

As a result, the CSPs of Phase 1 and simple Phase 2 studies often have few assessments, are small and less complex, and can be written quickly with only a few drafts. In contrast, a complicated Phase 2 or 3 CSP that has several objectives (eg efficacy, safety, pharmacokinetics and quality of life), assessment of multiple dose groups or treatment regimens, and perhaps includes sub-studies, may take months of discussion and consideration to develop. This means there will usually be numerous drafts and multiple rounds of revision as various stakeholders are asked to contribute their opinions on the design and activities to be performed.

Likewise, an IB needed in later stages of clinical development is a much more difficult document to write. The intention of the IB is to inform investigators who will be running studies about all available information on the PK profile, efficacy and safety of the drug being tested. By Phase 3, there is a wealth of clinical data available that needs to be condensed and consolidated into a brochure that is still easy and quick for the investigator to read. This takes much more skill and experience as a writer than the early editions of an IB. Thus, the demands on the team as a whole – but particularly on the medical writer – increase considerably with the rising complexity of documents in later stages of development. It is, therefore, important to ensure that the experience and skill of the medical writer is carefully matched to the demands of the documents in these different phases.

For investigational products that will be licensed for use in children, it is necessary to write a development plan focused specifically on the studies to be performed in children. This Paediatric Investigation Plan (PIP) in the EU, or Pediatric Study Plan (PSP) in the US, describes how clinical data will be obtained in studies involving children to support the

Document	Nature and purpose
Development Safety Update Report (DSUR)	A comprehensive annual review and evaluation of safety information relating to drugs under development, which must be revised annually as necessary
Clinical Study Protocol (CSP) amendment	Revisions to the original CSP that reflect changes in the design or investigational plan, eg due to practical problems in running the study or unexpected outcomes
Investigator's Brochure (IB) updates	Prior to the start of any new clinical trial, the IB must be updated with any data from prior studies; at a minimum, updates are required at least annually to reflect any changed information
Pregnancy prevention plan or programme (PPP)	A document laying out a set of interventions intended to reduce the likelihood of pregnancy during treatment with a medicinal product with known or potential teratogenic effects
Statistical Analysis Plan (SAP)	A detailed description of the statistical analyses to be performed on the data collected during the clinical trial, based on the statistical analyses described in the CSP. This includes the rationale and references for why particular statistical methods are appropriate for the planned analyses

Table 2: Documents to be authored during the conduct of clinical trials

authorisation of a medicine for them. These are not trivial documents, as they must provide detailed background information about what is known about the disease in children and what treatment options are already available; describe the measures to adapt the medicine's formulation to make its use more acceptable in children (eg use of a liquid formulation rather than large tablets); and address how the studies will cover the needs of all age groups of children (from birth to adolescence). Teams often underestimate the amount of time they will need to discuss, develop and agree on the content of their paediatric plans and it is important that the writing timelines plan for sufficient time to develop the document properly.

Documents Needed During the Conduct of a Clinical Trial

Once the clinical trials are running, the writing activities are far from over. Several documents need updating or writing throughout the course of a clinical programme, and many of these are written during the conduct of clinical trials (see Table 2). There are often amendments to the CSPs, which describe changes to the planned study or analyses, frequently because the original study design proves to be impractical, and the activities need to be adapted to make them more feasible or to increase patient recruitment.

Pharmacovigilance data that are collected during the conduct of a clinical development programme needed to be reported in a cumulative, ongoing manner in the annual Development Safety Update Report (DSUR). Updates to IBs need to be generated in preparation for the start of upcoming studies. The final statistical analyses of the trial data need to be defined in advance of looking at the data, and these are described in the Statistical Analysis Plan (SAP). It is important that clinical teams have all these documents on their radar to plan for them accordingly. There is nothing more frustrating than recognising a week before a new study is meant to be submitted that an important document, such as an updated IB, is not available. By mapping out the preparation of all these documents relative to the ongoing clinical studies, writing resources can be planned out well in advance and delays in starting new studies can be avoided.

Documents Needed after Completion or Termination of a Clinical Trial

Following completion of a trial, a comprehensive clinical study report (CSR) must be written that provides a detailed description of the results of the study, whether positive or negative. In addition to describing the methodology of how the study was run (including changes to the original plan according to the CSP), all of the information collected during the study needs to be reflected in this report. Again, depending on the clinical phase of development, a CSR can be a relatively short document (eg summarising a small Phase 1 pharmacokinetic [PK] study) or immensely complex and long (eg for a Phase 3 study with numerous assessment parameters and in a particularly complex therapeutic area). While the former may only take a few weeks to write, the latter can take 6 months or more for a team to craft and develop the storyline. Often it is simply the sheer amount of data that everyone has to wade through and digest that slows the process. However, it is important to give teams the time to do this properly – taking time to think ideas over and refine the messages through

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Document	Nature and purpose
Clinical Study Report (CSR)	A mandatory report covering the objectives, conduct and outcomes of the clinical trial. Note: the EU has recently defined a clinical trial report as a CSR pertaining to an interventional (rather than non-interventional) study
Clinical Trial Summary	A summary of a CSR, including a summary understandable to a layperson, to be uploaded onto a publicly available clinical trial registry (eg www.clinicaltrials.gov in the US or www.clinicaltrialsregister.eu in the EU)

Table 3: Documents needed after clinical trials have ended

a couple of iterations – since well-written text and more complicated thought processes take time to hone.

It is now obligatory to post a summary of the clinical trial results for studies performed in the US or EU on online databases for access by the general public. This summary must be submitted within 1 year of completion of the trial (ie last patient last visit, as described in FDAAA 801 Requirements in the US, and the detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities in the EU (2,3)). From the writing perspective, it is important to know that the reports posted on these public databases may not include any information that allows identification of any subject in a study, as outlined in the EMA policy 0070 (4). Hence, the medical writer should help their authoring teams understand potential implications of the information included in a CSR to avoid unnecessarily large efforts for redaction when creating these summaries (see page 63 for more detail about the EMA policy 0070 and its implications for public disclosure).

Documents Needed to Apply for Marketing Authorisation

After completion of the clinical development programme, the data collected need to be pulled together in a dossier that will be submitted as an application for marketing authorisation. These dossiers consist of summary documents written according to the guidelines of the common technical document (CTD). The clinical part of the CTD dossier comprises Module 2.5 (the clinical overview) and Module 2.7 (summaries of clinical pharmacology, biopharmaceutics, clinical efficacy and clinical safety) (see Table 4).

Writing these dossiers is the pinnacle of the medical writing challenge to synthesise numerous ideas and data points into a cohesive description of what is known about the medicinal product. The documents need to be written so that the regulatory reviewers can quickly understand what data are available from the clinical programme, and what these tell us about the PK profile, efficacy and safety of the drug, and the nature of its relative benefits and risks. Depending on the complexity of the product and the indication for which it is to be used, writing Modules 2.5 and 2.7 can take anywhere from 6-12 months (the writing and coordination of CTDs is discussed in more detail on page 32).

As part of the application dossier, the sponsor must plan for how any potential risk associated with use of the medication will be monitored for and minimised. This plan is laid out in the Risk Evaluation and Mitigation Strategies (REMS) document in the US (which is only required on request of the FDA) or the Risk Management Plan (RMP) in the EU (which is mandatory). As the name suggests, the document draws on all previous experience and reports of the drug to assess the main risks and to consider what would be appropriate precautions for ensuring appropriate monitoring and mitigation of those risks. The RMP also requires a summary for the layperson – ensuring that patients have full access to information about the risks of treatments they are being prescribed.

Documents Needed during Marketing (Phase 4)

In order to make health authorities, physicians, health practitioners and patients aware of a new drug – including its potential benefits and risks – the data gathered during the clinical studies are published in the form of posters, abstracts, manuscripts, patient information sheets and informative websites. There are very strict compliance rules around how marketing may be conducted, and what claims may be made in these documents.

In addition, specific material, including that derived from specially designed post-marketing (Phase 4) clinical studies, may be collected for the purpose of Health Technology Assessment (HTA) to gain specific knowledge about particular safety aspects of the drug, or to understand its performance in certain patient populations. HTA is the process by which national health authorities aim to assess the affordability of new drugs – comparing their benefits against their costs and that of alternative treatments.

Once a product is on the market, all records of reported safety events must be collated and assessed on an ongoing basis. This is done in the form of the periodic benefit-risk evaluation report (PBRER, previously the Periodic Safety Update Report, PSUR), as described by ICH E2C (R2) (5). The purpose of the PBRER is to harmonise the worldwide reporting of safety experience of a medicinal product after approval. Since the timing of when these reports must be submitted each year is regulated, preparation of these documents is often done under extreme time constraints between obtaining the data summaries for a reporting period and producing the final report. Since much of the data being assessed is in a similar format each time, it is possible to standardise the production and presentation of these data, which can go a long way to streamlining the writing process by allowing teams to focus their efforts on looking for safety signals, rather than agreeing on how to present the information.

Document	Nature and purpose
Module 2.5: Clinical Overview	A short (up to 40 pages) critical assessment of the clinical data culminating and a benefit/risk assessment of the product
Module 2.7.1: Summary of Biopharmaceutic Studies and Associated Bioanalytical Methods	A summary of the formulation development process, the *in vitro* and *in vivo* dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence and *in vitro* dissolution profile database
Module 2.7.2: Summary of Clinical Pharmacology Studies	A summary of the clinical pharmacology studies that evaluate human PK, pharmacodynamics and *in vitro* studies performed with human cells, tissues, or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK processes
Module 2.7.3: Summary of Clinical Efficacy	A summary of the programme of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought
Module 2.7.4: Summary of Clinical Safety	A summary of data relevant to safety in the intended patient population, integrating the results of individual CSRs as well as other relevant reports, such as the integrated analyses of safety that are routinely submitted in some regions. The aim is to clearly describe the safety profile of the product
Risk Evaluation and Mitigation Strategies (REMS) in the US or Risk Management Plan (RMP) in the EU	To succinctly describe how the risks of a product will be prevented or minimised in patients, provide plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine, identify risk factors for developing adverse reactions, and to explain how the effectiveness of risk minimisation activities will be measured

Table 4: Key clinical documents prepared to apply for marketing authorisation

Summary

Throughout the clinical lifecycle of a medicinal product, a myriad of documents are needed to effectively plan, run and then assess and communicate the outcome of the clinical studies performed. Many of these documents are complex compilations of data and thoughts, and also function in conjunction with other documents – meaning they all need to tell a consistent story.

It is important to have experienced stakeholders on the authoring teams, including a medical writer who has the experience with the document types to know how to advise teams on the needs of a particular document and to guide authors through the review and revision process. Planning well in advance and ensuring enough time is given to the authoring teams to allow them to think about, discuss and craft documents that accurately reflect what the data have to say, will ensure that these documents are fit for purpose while making the writing activities less arduous for everyone involved.

References

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3. Official Journal of the European Union, Communication from the Commission, Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (2010/C82/01)
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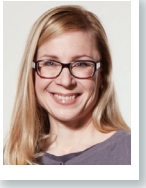
About the author



After receiving her PhD in Developmental Neurobiology, **Julia Forjanic Klapproth** started her career as a medical writer in the regulatory group at Hoechst Marion Roussel (later Sanofi) in 1997. Since then, she has been president of the European Medical Writers Association twice. In 2002, Julia co-founded Trilogy Writing & Consulting Ltd, a company that specialises in providing regulatory medical writing. In addition to managing the company as Senior Partner, she writes a wide array of clinical documents including study protocols, study reports, and the clinical parts of CTD submission dossiers.

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