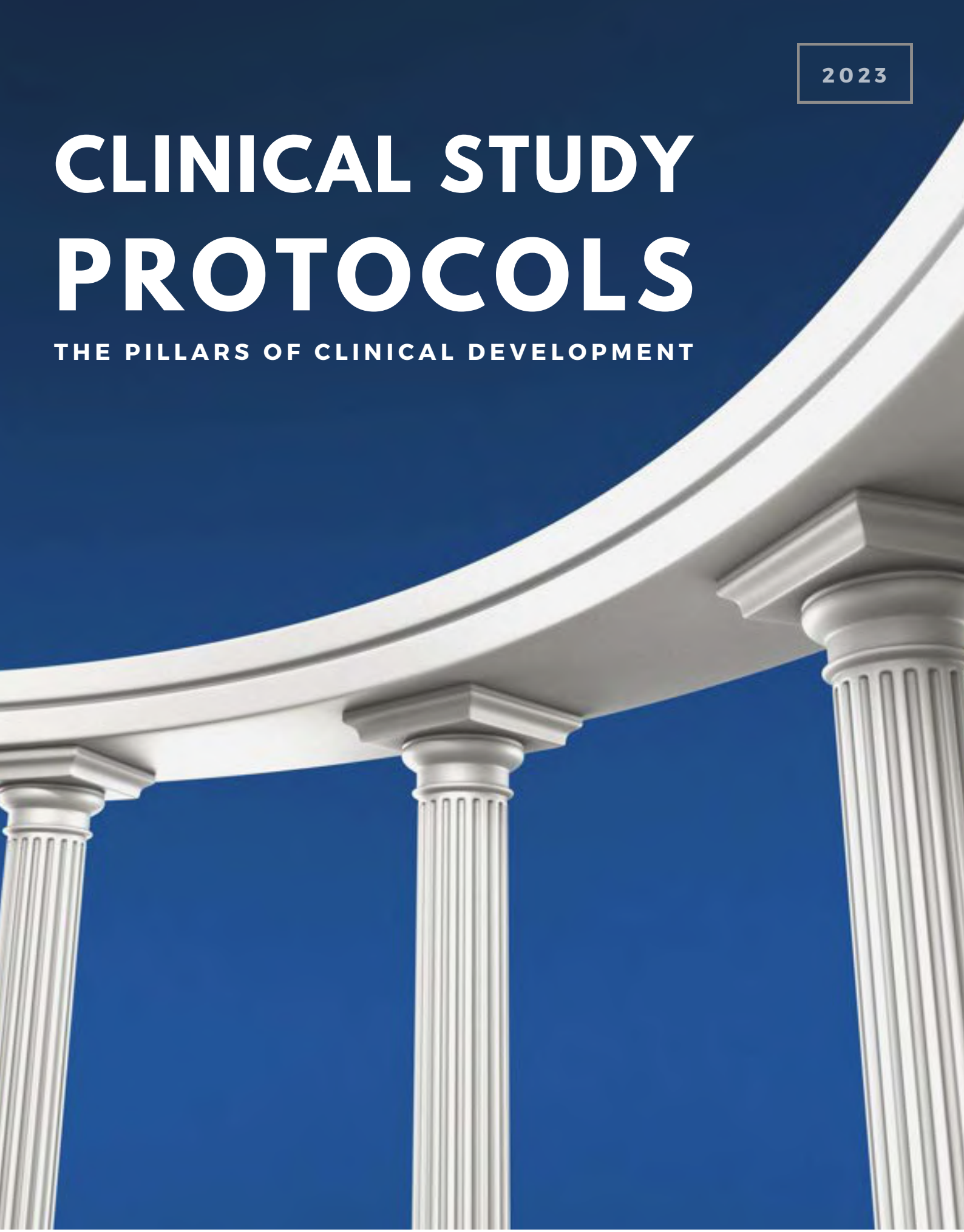
2023

CLINICAL STUDY PROTOCOLS

THE PILLARS OF CLINICAL DEVELOPMENT



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Clinical Study Protocols: The Pillars of Clinical Development

In their foreword, Julia Forjanic Klapproth from Trilogy Writing & Consulting and Jonathan Mackinnon from Parexel highlight the importance of raising awareness about improving clinical study protocols to drive efficiencies in clinical development

International Clinical Trials in association with Trilogy Writing & Consulting are delighted to welcome you to this Medical Writing Supplement, focusing on clinical study protocols.

In an industry seeking efficiencies and looking in every corner to reduce the time for drug development, we believe there is an unsung hero that needs to be recognised as a means to achieve both these things: a well-written clinical study protocol. In an effort to raise awareness about the far-reaching impact of well-crafted protocols, we have brought together a series of articles that focus on the reasons why study teams should be spending more time on making sure that they get their clinical study protocols right. Our goal is to help the industry recognise how well-written protocols can enhance study quality and speed up drug development.

As discussed in the opening article by **Julia Forjanic Klapproth**, the clinical study protocol serves as the cornerstone of a clinical study and yet poorly written protocols are still negatively impacting studies on a regular basis. Frequently this is because time is not adequately given to the human side of the writing process: the time needed to craft thought, for the team to discuss and bounce ideas around, and to find solutions and refine the study elements and design. The negative impact is only enhanced as increasing study complexity is causing a year-on-year increase in number of endpoints, assessments, and data points generated. How did we get here and what can we do? **Walther Seiler**'s article takes aim at the fundamentals – harmonised standards and content via protocol templates. Starting from the first ICH E6 guidance, Walther walks us through past and ongoing efforts to bring harmony to protocols and gives us a taste of where it might lead with the introduction of structured content in ICH M11. This narrative is complemented by **Jeff Garwin**'s perspective on the evolution of the protocol where there's a detailed analysis of the complexity drivers within a protocol and how protocol templates are critical tools for high-quality protocols. Best practices for using a protocol template and understanding the protocol development process are much needed and this article is important reading for all contributors to protocol development.

Natalie King and **Daniela Nakagawa** elaborate on how to reduce burden and increase compliance among study staff. In the face of rising complexity, they highlight four key pain points for study staff that well-written study protocols could reduce – eligibility criteria, the order of study procedures, discontinuation and study withdrawal, and patient reported outcomes. In another emerging protocol challenge, **Jonathan Mackinnon** addresses the rising popularity of master protocol studies and the need to revise the protocol development process to accommodate the additional challenges that this type of study design brings. Lastly – and still within the field of emergent protocol challenges – **Lisa Chamberlain James** discusses the new EU-CTR requirement: the lay protocol synopsis. In the article, Lisa sets out the requirements and challenges for the lay protocol synopsis and provides an intriguing perspective on what we may expect from this in the future.

Taken together, these articles provide an overview for how modern protocols are challenging medical writers and study teams alike due to the increased complexity and sophistication. They also discuss the guidance available to aid in developing protocols that overcome these challenges. The need for taking the time to get the protocol right cannot be overstated and are common themes that run throughout this edition. We hope that the content within provides some food for thought and, whether you are a writer or a reviewer, you pick up some points to consider for your next protocol.

Fix It Before It's Broken: Why Well-Written Clinical Study Protocols Get Drugs to Patients Faster

More than ever before, it's time to focus on getting protocols right from the start

Julia Forjanic Klapproth at Trilogy Writing & Consulting

In the world of drug development and approval, time is of the essence. We are developing medicines to help people with illnesses who need treatments sooner rather than later: every day makes a difference for someone suffering.

The COVID-19 pandemic showed us that it is possible to shorten the time to drug approval by focusing all resources in one direction. However, this is not a viable solution for standard drug development, where many drugs are being developed in parallel. By identifying inefficiencies in the system and eliminating these, it is possible to shave time off the drug development cycle.

Indeed, people have been trying to find ways to make the processes applied in clinical development more efficient for decades. This has included finding ways to ship material faster and more reliably, to better identify participants for clinical studies, and to clean and process data more quickly. There are also many technical areas that we can improve on, and each of these help speed things up.

Yet, there is an area that sits as a root problem in clinical development that needs to be improved: poorly written clinical study protocols. The protocol is the foundation of every clinical study. It informs investigators and study staff about the study's intention and provides a recipe for what needs to be done and how. It ensures that clinical teams at the sponsor and vendors are aligned on what the study purpose is and how the results will be analysed. Finally, it feeds into the clinical study reports and, ultimately, the clinical summaries for submission dossiers. If well written, it serves as the repository of intent for what was originally planned for each study in the lifecycle of that product's development.

If the protocol is not well written, users at all touchpoints may misunderstand the objectives, the design elements, and what they are meant to be doing. Poorly written protocols can lead to inconsistencies in the data collected as a result of differences in the timing of collection, the methodology of collection, and even the state of the participants during collection (e.g., fasting vs non-fasting). If the objectives are not clear, incorrect statistical methodology might be applied resulting in meaningless outcomes. Clinical studies have an ethical obligation to ensure they are contributing meaningful and relevant information; poorly run studies that produce meaningless outcomes are incompatible with a patient-centric approach to clinical research.

A poorly written protocol does not just impact one area of a study – it can impede teams in multiple domains, from setting up and running the study, to reporting on the study, and then applying for marketing approval. By the time a team gets to writing a submission dossier, it may struggle to adequately communicate and explain the rationale for critical topics, such as the dose

justification, if the protocols did not effectively communicate these ideas.

Moreover, the combined knowledge gained from all the studies of a clinical development program provide the necessary knowledge to determine the risk benefit profile of new drug products. If the data collected in those studies is inconsistent, has gaps, or has quality issues, then more studies will be needed to eliminate those problems.

In other words, having a clinical study protocol that communicates clearly and helps users find the exact information they need to make a decision or perform their task in a consistent way would kill many birds with one stone. It has the potential to effect transformative change by improving multiple, interdependent activities. It might not be a full panacea, but it certainly takes us in that direction. The question is, why is this so difficult to achieve?

There are multiple reasons that protocols do not end up as they should. One is that teams are often not aligned on what they want, and the protocol ends up trying to squeeze multiple agendas into a single study. Subject matter experts on teams sometimes lose sight of the fact that these studies are not academic excursions; they are being run to answer some specific questions to adequately inform the assessors about why a drug should be brought to the market. The more we try to ask in a single study, the more complex it becomes, the longer it will take to run, and the greater the chance for people to get confused about its purpose (1). As a result of a significant increase in the complexity of study designs over the last 20 years (2, 3), the quality of clinical data has decreased, and study costs have increased (4).

That's not surprising since it is much more difficult to explain the why and the how of a study that aims to answer multiple key questions than a study that aims to answer just one.

The teams who are designing these clinical studies need to be trained to focus on a few specific questions per study and not to go off on tangents.

This focus on quality was reinforced by the recent ICH E8(R1). Even in the case of adaptive study designs, each phase of the study still needs to stay clear on its intent, with well defined, objective criteria for moving on to the next phase.

This requires people who have sufficient understanding of the regulatory goals to provide a proper vision for an adequate development plan. It is not good enough to just grab the next physician who understands the therapeutic context and throw them into the foray, hoping they will design studies with a clear regulatory focus. Each protocol-writing team should have a session during the initial design stage to talk about how their study will comply with the SPIRIT guidelines (5).

Many stakeholders involved in writing protocols have not been given sufficient training in what makes a good protocol and what to focus on (6). By educating them on key guidelines and expectations, it would help ensure everyone is working to the same goals and would make the writing process more efficient.

With the increased complexity of studies, it has become even more important to have a good medical writer involved who will ensure the protocol presents a cohesive description of the study concept rather than a patchwork quilt of ideas. All too frequently the writing part of producing protocols is seen as 'just a bit of tidying up' to pull together the bits each function has thrown on that table, which can be done by anyone.

For all the reasons mentioned above, this document needs to be well crafted with concise writing that leaves no room for misunderstandings. In addition to honed writing skills, the medical writer needs to have insight on how this document will ultimately feed into downstream documents such as the clinical study report and summary documents. This helps them produce a protocol that makes writing these other documents more efficient.

Beyond that, the medical writer is at the heart of the protocol writing process. As they pull together all the pieces, they are best placed to recognise inconsistencies in the design concept or things that might be impractical. While each subject matter expert or functional area tends to review the protocol from their thematic perspective, the medical writer is often the only person who thinks about all the ideas holistically, considering how they all relate to each other. They need to have the wherewithal to be able to raise any concerns with the team and challenge them on things that do not make sense.

The medical writer must be able to do more than simply take the pieces and put them in place, without asking questions or thinking about how it all fits together. They should be the backstop, the person who works with the team to ensure that everything makes sense and fits together properly.

Another problem rampant in the industry is (to quote Mr Bergman) "there is never enough time to do it right, but there is always enough time to do it over." If we want to prepare protocols that will actively reduce protocol deviations and the need for amendments, we need to give teams sufficient time to think about the protocols before they go live!

Companies repeatedly request protocols be prepared in ridiculously short periods of time. This shows a complete lack of understanding of the complexity of the process to conceive a well-designed study and develop a well-written protocol. It also shows a deliberate misappropriation of time in favour of short-term start-up gain over long-term study risk mitigation. In most cases, this short-term gain is quickly spent on course-correcting activities that could have been prevented had more time been allowed at the beginning. If you want to be sure that a study site can do all the things required for each visit, you need to ask them. If you want to know how realistic it is to get blood samples from sites all over the globe to a centralised laboratory for analysis, you need to talk to the people who do this as their bread and butter.

That means that you need to build in time for conversations with those people, and even for them to review the protocol draft. In addition, the core team developing the study outline should have time to let ideas settle. Humans craft thought through an iterative process.

By discussing with each other and having the time to bounce ideas around, we come up with very good solutions to problems. But if that time is not available, then we will be stuck with the initial rough idea, warts and all, that never had the opportunity to be refined.

A team of experts with the knowledge and skills to do great things should be

> The medical writer should be the backstop, the person who works with the team to ensure that everything makes sense and fits together properly

given the breathing room to think things through. Forcing them to deliver a final protocol in a matter of weeks from start to finish is a guarantee for much longer delays later on (through amendments and deviations).

The process of writing a protocol requires several steps, which underscores the need for sufficient time to do it properly (1). It should start with creating an outline that is agreed on by a wide group of stakeholders (including sponsor management, site staff, and vendors); you want to get the concept in place before diving into the details.

It then moves into drafting a fully populated protocol that will be circulated for review among those same stakeholders, so they can evaluate the outline after it has been turned into a plan of action and confirm that this reflects their vision of the study. It is not uncommon in the second stage to realise that things were overlooked in the outline stage, which results in some (sometimes substantial) rejigging of the design.

Depending on the therapeutic area, teams may need time to go and look at examples of other studies that have been done in that area and collect ideas. Designing a Phase III study in a more complex therapeutic area in which treatment modalities are developing rapidly can take more time to figure out than for a relatively well-established treatment. It is important to allow for enough time and optimal conditions (i.e., not making teams squeeze this in while juggling multiple other competing projects) for the teams to think about the implications of the details and discuss the options with a clear mind.

In an industry striving to beat the clock, I am amazed at how much time is spent on fixing clinical studies once they are running, rather than aiming to get them right from the start. The cost of activities not considered essential to study objectives and endpoints is estimated to be between $4 and $6 billion each year (2).

The efficiencies to be gained by helping teams produce well-crafted study protocols are multifold. Investing a little more time in preparing a robust study outline and communicating this clearly and effectively will not only reduce protocol deviations and the need for protocol amendments, it will also reduce the time for writing study reports and clinical summaries, and make the assessment of these documents more efficient for agency reviewers.

More than ever before, it's time to focus on getting the protocols right from the start.

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Julia Forjanic Klapproth started working as a medical writer in the regulatory arena after getting her PhD in Developmental Neurobiology in 1997. She has since been President of the European Medical Writers Association (EMWA) twice (2001-2002, 2007-2009).

Julia is passionate about the value of good medical writing and is an experienced trainer of medical writers, regularly running workshops for EMWA, AMWA, DIA, and pharmaceutical companies around the world.

In 2002, Julia co-founded **Trilogy Writing & Consulting**, a company specialised in providing regulatory medical writing and she is still involved in writing and coordinating many documents, including study protocols, study reports, and CTD submission dossiers.

The Clinical Study Protocol: Will We Have a Harmonised Template?

The long-neglected protocol structure has finally received much-deserved attention

Walther Seiler at Bayer AG

Importance and Characteristics of Clinical Study Protocols

Preparing, running, completing, and reporting a clinical study is an enormously complex and costly endeavour that takes place in an increasingly regulated environment. This is reflected not least in the constantly growing number of different documents that are needed to accomplish this. Among these documents, the clinical study protocol (CSP) is certainly of key importance. The CSP's central role can be concluded from that document's diverse set of objectives, such as:

A. Definition of the study as a tool to generate scientific results
   - Justification for carrying out the study
   - Pre-specification of objectives and hypotheses (especially for confirmatory studies)
   - Outline of the analysis plan
   - Recipe for study conduct

B. Specification of ethical standards (especially subject safety) and administrative structures

C. Obligation of all CSP signatories ('contract')

The diversity of the CSP's objectives is also reflected in the diversity of its target audiences. While the clinical study report (CSR) almost exclusively targets the reviewers in the regulatory agencies, the CSP targets a diverse set of readers which includes not only the investigators and their staff (obviously the most important audience), but also other sponsor-external bodies (e.g., ethics committees, independent data review committees, regulatory authorities) as well as sponsor-internal readers (e.g., staff involved in managing and monitoring the trial conduct and in preparing associated documents such as the statistical analysis plan [SAP] or the CSR).

In brief, the importance of the CSP can hardly be overestimated as it not only steers the success of a particular study, but also sets the stage for a number of subsequent documents critical to the success of the underlying clinical development programme as a whole.

Content of Clinical Study Protocols

Given the importance of any CSP, formal regulation about the type of information it needs to include came remarkably late. Let's take a brief look back at how this situation evolved.

In 1996, Guidance E6 on Good Clinical Practice (GCP) was released by the International Conference on Harmonisation (ICH) (1). This guidance contained a list of items to be covered in each CSP (2). While the 2016 update of E6 (R2) did not change the section on CSPs, the subsequent E6 (R3) points out that "the most important tool for ensuring human subject protection and high-quality data is a well-designed and *well-articulated* protocol. *The clinical trial protocol … should be clear, concise*, and operationally feasible." (My emphasis).

In parallel to this evolution of ICH GCP, CDISC published its Protocol Representation Model (PRM) in 2010 which contained a comprehensive list of protocol elements and their logical inter-dependencies, aiming at machine readability of the CSP. As such, the PRM was not meant to serve as a specific template for the CSP document and is therefore of limited relevance for medical writers.

In 2013, the SPIRIT Statement was published. Based on a systematic assessment of past CSPs, this list of minimum content for a CSP was unprecedented with regard to comprehensiveness. Indeed, the ever-increasing list of content expected in a CSP reflects the ever-growing level of regulation seen for almost all aspects of clinical development.

Of note, while the level of granularity and specificity of CSP content has grown considerably over the years, no formal guidance on how to structure and present this complex information

in a CSP document was available until recently. This, by the way, contrasts to the CSR for which structural guidance has been available in the form of ICH E3 for a long time; although formally not meant to serve as a template, ICH E3 has been viewed and used as such by many. Regulatory agencies were seemingly more interested in harmonising CSRs than in properly shaping CSPs.

Format of Clinical Study Protocols

The Early Years

For a long time, a Google search for 'CSP template' or the like would result in plenty of hits. However, the templates made available to the public are typically geared to specific types of studies (e.g., for a particular therapeutic area, for a particular institution or for a specific phase of clinical development), thus strongly limiting their general applicability. More importantly, these templates were offered by non-authoritative sources, thus lacking global acceptance.

As a consequence of this lack of global standardisation, there was considerable and long-lasting variability across the industry in how CSP documents were organised and structured.

As a side note, the originators of ICH E3 must have had a similar impression when they included in their CSR guidance the explicit advice that "in each [CSR] section describing the design and conduct of the study, it is particularly important to clarify features of the study that are not well-described in the protocol".

As a further side note, I am curious whether this important aspect will be sacrificed in the current attempts at end-to-end automation of document content from study concept to MAA, or whether eventually ways will be found to accommodate options to improve

document quality along the documents' value chain - in the interest of human readability. Of course, if protocols were well crafted, there would be no need to compensate for poor descriptions in the protocol when writing the CSR.

The long-lasting lack of a globally accepted standardisation of CSP structure frequently resulted in nightmares, especially for investigational staff using the CSP for study conduct. Active study centres may be involved in multiple clinical studies at the same time, each of which might be sponsored by a different pharmaceutical company.

This may result in the same type of study procedure being described in a different manner, and these descriptions being located in very different sections of the CSP. It is not difficult to see how inefficient and error prone this situation is for the CSP user.

TransCelerate

Fortunately, long-awaited deliverance appeared on the horizon not too long ago. Interestingly, it was not the regulatory authorities (who are otherwise not reluctant to regulate so many aspects of clinical development), who first came to the rescue, but the pharmaceutical industry. In November 2013, TransCelerate included a harmonised CSP template into its list of initiatives (3). In August 2015, the first draft of what soon became widely known as the Common Protocol Template (CPT) was sent to selected communities for review and comment.

This draft was followed by an iterative series of public releases, each time with the opportunity to submit comments. While the first CPT draft had been very immature indeed (e.g., it completely lacked specifications on CSP amendments), subsequent releases reflected step-wise improvements, with the current version (v9.0, released October 2021) truly representing a sound, solid and comprehensive CSP template with extensive guidance text on how to populate the various CSP sections. As an accompaniment to the CPT, a set of library documents harbour CSP information for specific study types (e.g., paediatric trials) that would overload the main CPT file aimed to be applicable to nearly all types of clinical studies.

Although TransCelerate is continuously open to input from regulatory bodies around the world, the CPT remains predominantly shaped by the pharmaceutical industry. This may explain why substantial effort was needed to align with a CSP template released a little later by the US FDA/NIH (initial release March 2016). Fortunately, this discrepant parallelism did not last for long. It was, however, to be followed by a similar duplication, described below.

A valuable aspect of TransCelerate's CPT is that it is embedded in an ambitious set of templates for several clinical documents intended to pave the way for content re-use from CSP to CSR and beyond. For this, the TransCelerate templates for CSP, SAP, and CSR are also available as 'technically enabled' versions to eventually automate such a process.

> Of note, while the level of granularity and specificity of CSP content has grown considerably over the years, no formal guidance on how to structure and present this complex information in a CSP document was available until recently

The CPT certainly does not revolutionise the way a resulting CSP is structured and populated. However, the biggest value of the CPT lies in it's potential to standardise CSPs around the globe.

This standardisation is the result of the wide acceptance of the CPT, which is based on the fact that the CPT reflects hands-on experience in CSP design accumulated over decades across the pharmaceutical industry. While the CPT package may not be perfect in all aspects, it is a fair statement that anybody using the CPT and associated libraries for CSP development has a very good chance of ending up with a well-received and well-usable document that follows a structural standard that is now widely accepted. This last aspect is a key argument for many companies to implement the CPT; if they do not, they will clearly be disadvantaged when competing with CPT-using sponsors for investigators (and their patients!).

Seemingly, this could be the happy end of an eventful story. However, the saga continues with the appearance of a new player on the stage of CSP templates.

ICH M11

After decades without visible formal participation in attempts to develop a globally accepted CSP template, ICH published its final concept paper of M11 on *Clinical Electronic Structured Harmonized Protocol* in November 2018. This can be viewed as a surprising move, given the fact that with the CPT a widely accepted CSP template had just become available.

In 2019, an initial draft of the ICH M11 template was circulated in selected communities for upfront review; it is noteworthy that this draft exhibited considerable differences to TransCelerate's CPT. After further interim versions, the project has meanwhile reached the formal Step 2 of the ICH process during which a more mature draft of ICH M11 has been released for public consultation until early 2023.

Of note, this current draft is much more aligned with the CPT than the initial draft. However, some relevant differences remain. For example, part of the beauty of the CPT structure lies in the offloading of non-study-specific information (e.g., the definition of AEs) into the CSP appendix; this applaudable approach is not systematically applied in the current draft of ICH M11.

Further notable differences include the lack of seasoned or even required CSP sections in the current draft of ICH M11 (e.g., study background, recruitment strategy, dissemination of data) and its rather minimal use of guidance text for the template user compared to TransCelerate's CPT. By the way, the proper definition and consistent use of certain key terminology (e.g., 'rationale' vs 'objective' vs 'purpose') seems to be a challenge for all templates.

Conclusion

After a long period without a widely accepted CSP template, TransCelerate deserves the credit for having closed that gap for the first time.

The subsequent advent of ICH's CSP template M11 created the unexpected situation of a parallelism of two separate, although similar, CSP templates, each from an authoritative source and each with the claim of global reach. It remains to be seen how this situation will finally be reconciled.

Notes

1. *Later re-named to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*
2. *Interestingly, this list was far less detailed than the description of the CSR methods part in ICH E3 released a little earlier (1995).*
3. *Visit: transceleratebiopharmainc.com/*

Berlin-based **Walther Seiler,** PhD, ELS is a regulatory medical writer with more than 30 years of experience in an international CRO and a global pharma company. For many years, his responsibilities included the maintenance of his company's templates for CSRs and CSPs. Currently, he serves at **TransCelerate** as one of the CPT Content Stewards.

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Perspective on Evolution of the Clinical Study Protocol

This article discusses the ongoing evolution of the clinical study protocol looking forward from 30 years' experience in clinical and regulatory development

Jeff Garwin at PPD, part of Thermo Fisher Scientific

Regulatory Drivers of Protocol Evolution

Arguably, the regulatory impetus for the modern protocol originated in the US with the passage in 1962 of the Kefauver-Harris Drug Amendments to the Federal FD&C Act (1). With these amendments, pharmaceutical companies had to provide substantial evidence of effectiveness for a product's intended use through adequate and well-controlled studies. Furthermore, for the first time, the FDA was required to approve a marketing application for a drug to be marketed. Finally, the US Secretary of Health, Education and Welfare was required to establish rules for investigation of new drugs. The pressures of FDA rulemaking and nonbinding guidance documents have been shaping the content of the protocol ever since. Functionally similar regulatory requirements have developed nearly contemporaneously in Europe.

The Kefauver-Harris amendments required for the first time that adverse events be reported to FDA, and in 1981 formal standards for the Protection of Human Subjects and Institutional Review Boards (IRBs) were strengthened. Drug sponsors now had to show results of preclinical testing and what they propose for human testing, by way of an investigational new drug application (IND). A clinical study (study in humans) can begin only after the applicable IND is reviewed by the FDA and an IRB has reviewed the protocol.

In practice, the FDA review of individual protocols focuses on the adequacy of risk management for study participants. FDA's attention to the adequacy of study design to achieve development objectives can be limited to the assessment of the benefit-risk evaluation for conducting the study.

The IRB (or independent ethics committee [IEC]) reviews are similarly focused. For these reasons, the regulatory and safety stakeholders are secondary audiences of the protocol.

Over time, the standards for what constitutes an adequate and well-controlled study and what constitutes adequate protection of the rights and welfare of human subjects have evolved. The requirement that studies be adequate, well-controlled, and independent of each other resulted in the current paradigm of an 'arm's length' relationship between the drug sponsor and the individual investigators and their study staffs.

The protocol became the primary tool for ensuring consistency of study conduct across independent study sites, according to the sponsor's programme plan.

Complexity Drivers of Protocol Evolution

Study complexity has been a significant driver of protocol evolution; increasing numbers of different kinds

of assessments have resulted in greater administrative and operating burden on investigators, study site staff, participants, and study monitors (2). Drivers of assessment complexity include the following:

- Increased specificity of diagnostic eligibility criteria: e.g., new biomarkers and technology for assessing them
- Technological advances in imaging technologies for assessing disease staging and progression
- Increased number of medical disciplines (including surgical and diagnostic) being involved in clinical trials
- The introduction of biologics as investigational products, commonly requiring assessments of immunogenicity and autoimmune sequelae
- Increased frequency of using novel biomarkers as potential surrogates of therapeutic efficacy
- Increased number of patient-reported outcome assessments
- Increasingly common health economics or medical resource utilisation assessments
- Increasingly common genetic assessments including related technologies
- Changes in standards for statistical analysis; e.g., the mandate for including estimands in the protocol
- Incorporation of more sophisticated data collection systems

Recent research showed that increasing the number of clinical trial sites can result in decreased standardised effect size of randomised controlled trials of opioid efficacy (3). Inconsistencies in study conduct across study sites have long been assumed to add variability to study data. To reduce such inconsistencies, protocols have become increasingly comprehensive and specific in standardising trial methodology, implementation, and monitoring.

Drug sponsors delegate many or most responsibilities for conducting clinical trials to Contract Research Organisations (CROs), including writing/contributing to protocol development, identifying study sites, training investigators and study staff, setting up EDC systems, providing clinical supplies and laboratory testing, monitoring data collection and study conduct, and analysing data.

This delegation of responsibility adds another communication layer of complexity to the development of protocols and study conduct,

as evidenced by development communication plans between sponsors and CROs.

The Protocol Template: A Tool for High Quality Protocol Development

In this supplement, there is a good discussion of the historical convergence of the pharmaceutical industry on a common protocol template (4). Protocol templates are key tools for improving the quality and consistency of protocols across the following dimensions:

- Consistency of content – the template provides a checklist for critical content to be addressed in the protocol. For an extensive discussion of the value and use of checklists, consider reading *The Checklist Manifesto* (5). The most useful templates include author guidance for the contents of each section
- Consistency of flow – there is a logic in the order of presentation
- Consistency of format – there is consistency of writing conventions across protocol sections as well as consistency of heading structure and location of content across protocols
- Consistency of navigation – with Microsoft Word as the de facto standard word processing programme, it is easy to navigate between sections of the protocol using internal hyperlinks and the navigation pane
- Consistency of rhetorical style – the most useful templates include guidance for the author on clear and concise presentation across the sections of the protocol

Best Practices for Using a Protocol Template

Remember your primary goal: to lay out a detailed plan to be followed consistently by those responsible for study conduct. Then, provide the appropriate level of detail. For example, in the sections on background information and rationale for the study design, limit the presentation to those elements required to understand the purpose behind each element of study conduct. Too much detail can interfere with comprehension.

Minimise inherent protocol complexity by minimising the number of objectives and the number of assessments, consistent with the study phase. The larger the number of assessments, the greater the burden on study sites, monitors, and participants. The greater the burden, the more difficult the recruitment of investigators and participants, and the lower the retention of participants to the end of the study on study treatment without protocol deviations.

In a Phase II study, consider limiting the number of patient-reported outcome assessments to instruments validated for the intended indication, or to instruments already appearing in approved labels. For Phase III studies, consider including only validated assessments that have demonstrated utility in Phase II and that have a high likelihood of inclusion in the final approved label. The most rational goals for other assessments, unlikely to appear in the label, would be for publications that might guide physicians in their use of the marketed product or to guide new validation studies.

Follow lean authoring principles and simplify the writing. The simpler the writing, the easier it is to understand. Understanding the assessments, both their purpose and mechanics, is important both for study site staff who will be performing them and for the sponsor or CRO personnel who will be implementing the operational aspects of the protocol, such as site training, clinical supply, data collection, data management, statistical analysis, and study monitoring.

The first principle of lean authoring is to avoid repetition. Repetition increases the likelihood that inconsistencies will be introduced that will need correction through protocol amendment. Protocol amendments are costly in time and money and can reduce the scientific integrity of the study. The simplest rule is, provide detailed descriptions in only one section of the protocol.

Everywhere else, make a high-level summary statement and hyperlink to the section where details can be found. Examples of violations of this principle include multiple descriptions of the same study assessment and repeating content in the body of the protocol that is primarily located in the schedule of activities.

Simplify writing by the following techniques, all of which will reduce the reading grade level of the document. Protocols written at a college or higher reading level risk poor communication to staff of lower educational attainment or for whom English is a second language. The Microsoft Word programme has a function that calculates readability statistics; to achieve a lower Flesch Kincaid grade level:

- Choose short words over long words. You may be surprised at what you can convey with words of two syllables or less
- Keep sentences short and simple. Avoid multiple clauses and parenthetical expressions
- Use the active voice

Use a focused authoring approach, starting with understanding the context of the protocol within the clinical development plan and ensuring that the protocol is fit for purpose. Consider the following practices:

- Focus on the primary audience and make it easy for them to understand and adhere to the procedures specified in the protocol
- Ensure that all content in each section is necessary, clear, and purposeful.

- Consistently follow a journalistic paradigm within sections and paragraphs by starting sections and paragraphs with the highest-level statement and working down through lower level instructions or descriptions
- Use parallel structure within sentences, between paragraphs, and between sections
- Write precisely and concisely. Use bulleted lists or tables instead of lengthy sentences or paragraphs

Evolution of the Protocol Development Process

Increases in complexity and scale of clinical trials, together with increased early involvement of logistical personnel in study initiation, are increasing pressures to improve the process of developing protocols. Where formerly a single medical director from the drug sponsor might have written a protocol, today the protocol is developed by teams of subject matter experts (SMEs) led by clinical scientists or medical writers.

Often, a different collection of SMEs is responsible for writing a study outline before the protocol is written (6). If the sponsor delegates responsibilities for conducting a study to a CRO, CRO personnel may serve as SMEs both for the study outline and the protocol itself. The protocol contents and development are changing in the following ways:

- A study outline is being used to rapidly refine the main elements of the study design: objectives, assessments, endpoints, key inclusion and exclusion criteria, use of electronic data collection techniques, treatment arms, main statistical approaches, complete schedule of events
- SMEs in clinical trial management, digital data collection and data management, clinical supply, and laboratory services are increasingly contributing directly to the refinement of the study outline and the protocol itself
- Stable study outlines are used to qualify study sites and can also be used as the starting point for developing EDC systems for clinical data, as well as the starting point for developing the clinical supply strategy. Feedback from investigators based on the stable study outline is being used to refine the study outline and as input into the final protocol. Such early use of study outlines can reduce the time between start of protocol development and study initiation
- While there is now substantial agreement within the pharmaceutical industry on the level 1 and level 2 headings of a protocol, the level of detail presented within the protocol body is evolving. Following lean authoring principles, reference is increasingly made to protocol appendices or external documents that provide details important to the conduct, review, or analysis of the study, such as the investigator's brochure, study manuals, monitoring plan, review board charters, statistical analysis plans, and information that is not study-specific (e.g., definitions of adverse events, contraception requirements, investigator responsibilities)

Conclusion

Protocol templates and the protocol development process will continue to evolve in response to increases in study complexity and changes in regulatory oversight.

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Authoring Protocols to Reduce Burden and Increase Compliance Among Study Staff: Perspectives of a Study Monitor and a Medical Writer

A call to medical writers to be bold and innovative in finding ways to make protocols clear and user friendly

Natalie King and
Daniela Nakagawa at
Azur Health Science

The Problem with Complex Protocols

Over the years, protocols have become increasingly complex. The number of countries and sites where Phase II and III protocols are conducted has grown substantially since 2009, with on average three times more data collected compared to ten years ago (1, 2). This complexity has increased the burden on site staff conducting clinical research. Understandably, with this increased workload, site performance has decreased (3). Any means by which this burden can be limited will positively impact site performance, compliance to study procedures, data quality, and, ultimately, the patients for whom the studies are run.

Increasing Compliance Through Good Medical Writing

One way to decrease the burden on the site staff is by authoring clear and user-friendly protocols. Common issues experienced by the primary users are: difficulty finding the information they need, ambiguity, inconsistencies, and lack of detail in topics essential to conduct the study. Medical writers authoring protocols must ensure that the document is well written and contains all the necessary information whilst following strict regulatory guidelines. Equally important is to keep the users of the protocol in mind when authoring and reviewing protocols.

Putting oneself in the shoes of an investigator recruiting a participant or a study monitor presenting the study at a site initiation visit can help identify areas where extra clarification is needed. Medical writers can ask themselves if the information presented is sufficient to replicate what is explained in the protocol or if anything could be written differently.

This article focuses on what medical writers can do to reduce the burden on the site staff and participants to

improve compliance. Specifically, we invite medical writers to be bold and innovative on four sections of the protocol: the Inclusion and Exclusion Criteria, the Schedule of Procedures, the Discontinuation of Investigational Product and Withdrawal of Study, and the Patient Reported Outcomes (PROs). At the end of the article, we propose a checklist of critical questions to ask when authoring a protocol.

Inclusion and Exclusion Criteria

Inclusion and Exclusion Criteria is one of the protocol sections that raises many issues for the study monitor explaining these details to the staff implementing the study. Long and ambiguous criteria with multiple interpretations lead to misunderstandings that waste time, lose potential participants or, at worst, result in enrolling ineligible ones. There is no need to reinvent the wheel regarding the inclusion and exclusion criteria. The TransCelerate BioPharma organisation or the Clinical Data Interchange Standards Consortium offer therapeutic libraries with criteria specific to a disease (4, 5). Some of these lists of criteria have subsections that facilitate their reading, such as age, sex and weight, type of participants, prior or concomitant therapy or both, among others.

Medical writers are rarely involved in drafting the list of criteria and, more commonly, are presented with a list frequently considered final by the clinical teams. Yet, if these criteria are confusing or poorly worded, it is the responsibility of the medical writer to work with the team to increase their clarity and conciseness. We suggest the following changes to the list of inclusion and exclusion criteria to aid readability and user-friendliness:

- Split the lists into study critical and standard (e.g., contraceptive requirements) criteria. Among the critical criteria, list the ones that could cause confusion first and explain how to proceed using 'if *X*, then *Y*' sentences in all of those cases
- Among the standard criteria, move the generic information, such as the definition of 'woman of childbearing potential' or 'highly effective contraceptive methods', to the appendices
- Tabulate the lists of permitted and prohibited therapies and any period associated, place these tables in their corresponding protocol section, and cross-refer to this section in the list of criteria; state if the list of therapies is non-exhaustive

Schedule of Procedures

Site staff need protocols that are easy to understand and follow. Writing short paragraphs, breaking down large blocks of text with bullet points, and creating tables and figures will increase readability, save time, and avoid confusion. Still, protocols convey so much complex information that simplifying the study design by presenting it in a table like the schedule of procedures is sometimes not enough. This table often misses crucial information, such as the order in which procedures should be performed or includes a long list of footnotes that leave staff combing for the information they need, thus wasting their time.

It is difficult for medical writers and the study team to strike a balance between including essential information in the table and not overloading it. One way to tackle this dilemma is to make more use of figures and flowcharts in protocols.

In addition to the study schema, these visual elements can reinforce critical steps in the schedule of procedures, such as the order in which assessments should be performed, as illustrated in **Figure 1**.

A salient visualisation like this will make the order of procedures immediately accessible instead of searching for it in the body text or among footnotes.

Discontinuation of Investigational Product and Withdrawal from Study

Even if explained in short paragraphs or broken into bullet points, the *Discontinuation of Investigational Product* and *Withdrawal from Study*

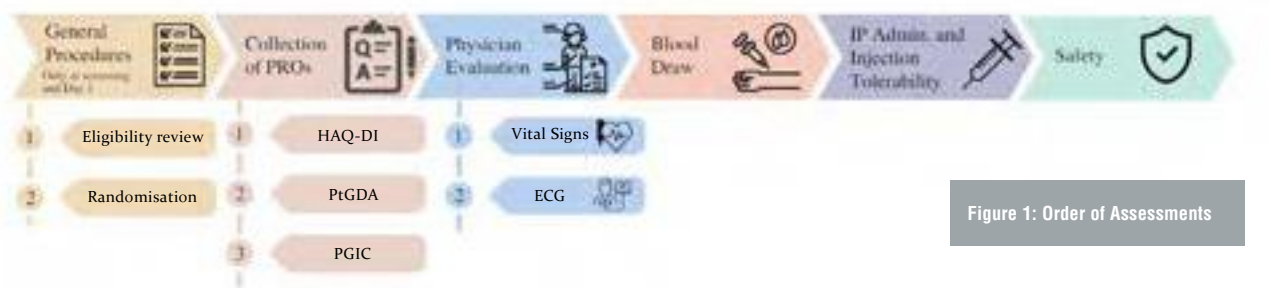

Figure 1: Order of Assessments

ECG, electroencephalogram; HAQ DI, health assessment questionnaire-disability index IP, investigational product; PGIC, participant global impression of change; PROs, patient reported outcomes; PtGDA, participant global disease activity.
Notes: Physician evaluations can be performed in any order, but ECG should always be obtained after vital signs

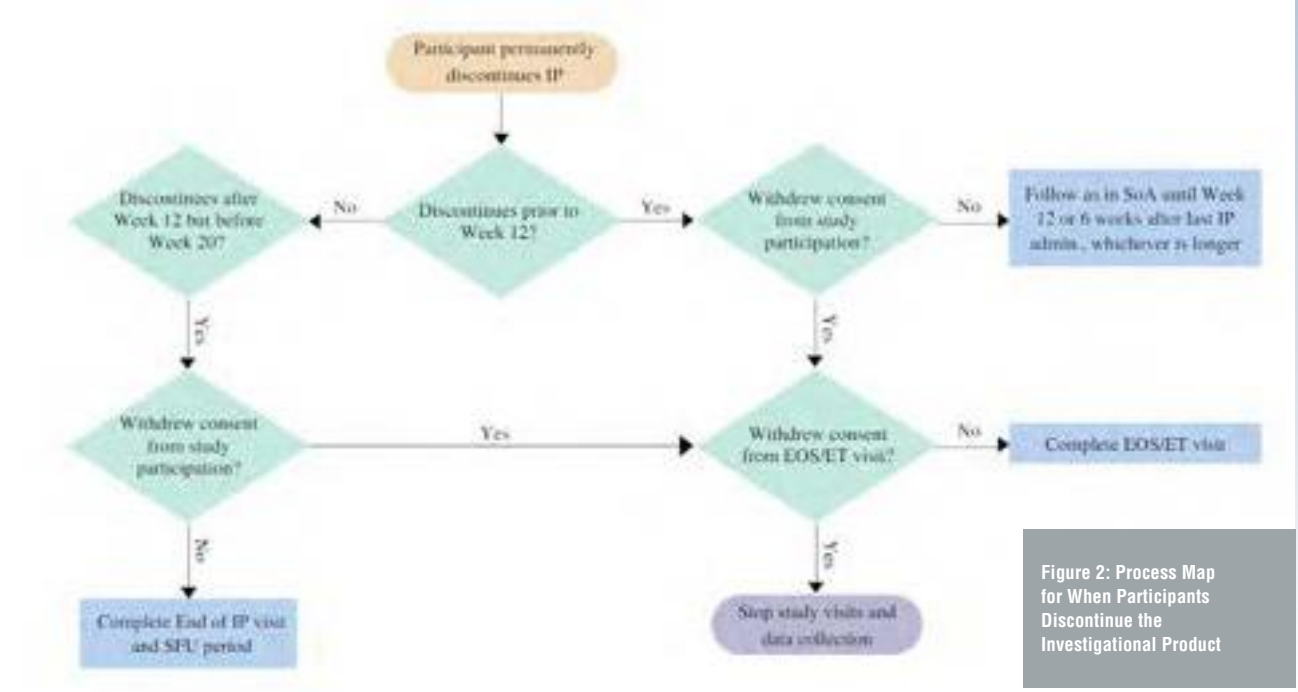

Figure 2: Process Map for When Participants Discontinue the Investigational Product

EOS/ET, end of study/early termination; IP, investigational product; SFU, safety follow-up; SoA, schedule of assessments.
Notes: In this example, Week 12 is the visit week on which the primary assessment of the efficacy endpoints is performed, and Week 20 is the visit week on which participants receive the last administration of IP

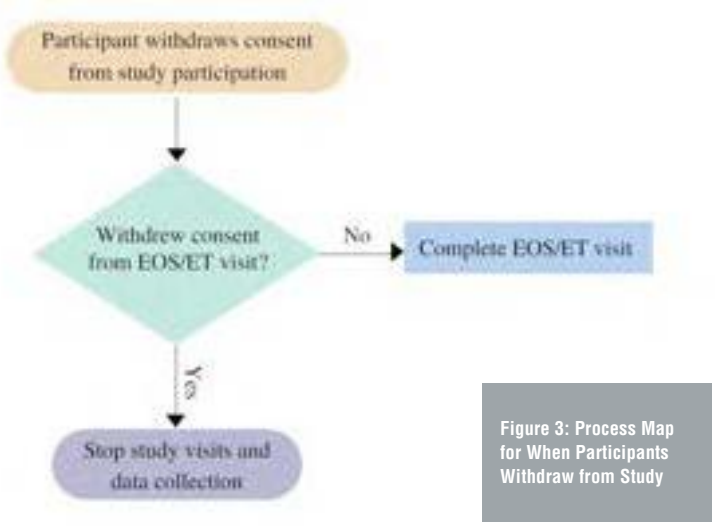

Figure 3: Process Map for When Participants Withdraw from Study

EOS/ET, end of study/early termination

sections usually result in wordy text that leaves site staff puzzled about how and when to proceed in these cases.

In other instances, these sections are so briefly explained that less importance is given to them by investigators, which can lead to missed follow-up visits and participants lost to follow-up as they are unaware of having to come back (if applicable) to the site.

Process maps like the ones in **Figure 2** and **Figure 3** will increase understanding of how to proceed when subjects discontinue taking the investigational product or withdraw from participating in the study.

(Electronic) Patient Reported Outcomes

Patient reported outcomes (PROs) are being used more and more in clinical studies to collect vast amounts of data from the participant's perspective and support study outcomes. However, despite their importance, the amount of practical information provided in the protocol about their administration varies greatly. Consequently, compliance rates for PROs are often poor. A recent review of randomised control trials in ovarian cancer reported rates of preventable missing PRO data of 17% to 41% (6). Some reasons for this could be:

- The high burden on participants, leading to non-completion of their questionnaires
- Lack of clear guidelines on how to administer them, leading to missing questionnaires at the site
- Participants having difficulty completing electronic PROs on their devices, such as geriatric populations not accustomed to smartphones or tablets

A detailed protocol section on PROs could resolve many of these issues. This section can specify the following critical but often overlooked information:

- Their format: paper or electronic
- The order in which they should be completed
- Their use in the primary or secondary endpoints: This should be clearly stated to ensure that site staff pay particular attention to their compliance and adapt their explanations to the participants accordingly
- If an inclusion or exclusion criterion depends on them: An adequate explanation in the protocol will allow the selection of participants who are fully aware of the requirements for completing PROs from the outset
- The need for participants to be technologically literate when electronic PROs are used
- Their correct versions and availability
- A reference to their manual

To help implement these points, we suggest the following standard statements that can be added to the protocol template to aid in the consistency and completeness of the PRO instructions:

- *A list of PROs to be assessed and the order in which they should be collected is in the Schedule of procedures (Section [section number])*
- *Patient Reported Outcomes will be provided in [paper/electronic device], and instructions will be attached to the corresponding questionnaire or form. A link to each PRO is provided in their description (Section [section number]) and the references (Section [section number])*
- *Participants should complete the questionnaires or forms by themselves in a quiet environment*

(Instructional text: Erase the following sentence if paper PROs are not used.):

- *[Paper] PROs will be provided at the study site*

(Instructional text: Erase the following sentence if paper PROs are used.):

- *Participants will complete the questionnaires at [home, the study site, or both] on an electronic device*

The PRO Extension of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) of 2013 was created to "provide recommendations for items that should be addressed and included in clinical trial protocols in which PROs are a primary or key secondary outcome" (7, 8, 9).

Combined with our suggestions above, we encourage medical writers to use these valuable guidelines and make the study teams aware of their importance during the protocol authoring and review process.

In conclusion, high study complexity does not have to translate into complicated protocols that burden the investigator, the site staff, and the study monitor. There is much that medical writers can do to improve how information is presented in protocols and increase site staff compliance.

Better compliance to study procedures means higher quality data and getting new medicines to the patients who need them, in less time.

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Author's Checklist: Key Questions to Ask Yourself When Authoring a Protocol

Inclusion/Exclusion Criteria

1. Are the inclusion and exclusion criteria explained without ambiguity? Could different people have different interpretations of any of the criteria?
2. Have the study critical and standard criteria been split to make it easier for site staff to see the key study-specific criteria?
3. Have lists of permitted and prohibited therapies been tabulated?
4. Is it stated whether the lists of permitted and prohibited therapies are exhaustive?

Schedule of Procedures

1. When reading the description of study procedures, is all the information needed to replicate the protocol present? Are any details missing, such as the order in which procedures should be followed (if applicable)?
2. Is all the information from the footnotes present in the text?
3. Would visual elements such as in **Figure 1** improve the presentation of the study procedures?

Discontinuations and Withdrawal from the Study

1. Are the procedures for patient discontinuation and withdrawal explained thoroughly and, in enough detail, to cover a lot of common scenarios?
2. Would a process map like the one presented in **Figure 2** and **Figure 3** improve the explanation of the patient withdrawal and discontinuation procedures?

(Electronic) Patient Reported Outcomes

1. Have the PROs been explained in enough detail for site staff to understand what will be required of them and their patients?
2. Has the format (paper or electronic) been specified?
3. Is it stated if PROs are part of the primary or secondary endpoints?
4. Are the correct versions of PROs included in the protocol appendices?
5. Has the PRO manual been referenced to ensure site staff know where to find further information?

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Taking the Time to Develop a Protocol for Master Protocol Studies – Why Planning Matters

As study teams look to adopt these designs, they will need to complete additional preparation steps if they want a smooth and seamless protocol development process

Jonathan Mackinnon at Parexel International

'Master protocol studies' are studies with a single overarching design developed to evaluate multiple hypotheses and improve efficiency through standardisation and uniformity (see **Table 1**) (1, 2).

A common master protocol infrastructure includes standardised operational structures (such as patient screening, patient enrolment, data collection, data analysis, and study management) that are augmented by substudies intended to evaluate different participant populations, interventions, or a combination of both.

These master protocol designs are most commonly classified as basket, umbrella, or platform studies, and are frequently combined with adaptive design or complex statistical analysis components (3).

When correctly applied, master protocol designs have been shown to provide a more structured and sustainable approach to clinical study evaluation and to be economically beneficial compared with more conventional trial designs (4, 5). Although master protocol designs have been around for some time, their successful use during the COVID-19 pandemic has accelerated their adoption (6, 7).

This success has not come without challenge. The limited practical experience in developing these complex protocols has required study teams to learn how to focus limited resources on the critical elements that matter most, and avoid non-critical elements that can easily overburden a study when applied across all substudies (8).

To achieve this, it is necessary to adapt the methods by which study teams develop the study design and the protocol to avoid 'rework traps', where substantial changes to the study design or protocol are needed mid-development. This article looks to highlight the key planning steps prior to starting protocol development.

Establishing the Study Design Outline

The crucial first step to any successful protocol is to establish the study design outline that provides a high level description of the study population of interest, intervention, comparator, outcome, and study design. For master protocol studies, additional considerations need to be confirmed prior to protocol development to make sure:

1. All study team members and other stakeholders agree on the overall purpose, rationale, and structure of the study and each of its substudies
2. Risk of substantial study redesign or document restructuring mid-protocol development are mitigated
3. Protocol quality is enhanced by making sure that the document is designed with quality from the beginning

These considerations are described below and are based on the EMA Complex Clinical Trials guidance (9).

Risk-Benefit Assessment for Employing the Proposed Design

At the beginning of the article, a few of the key benefits of deploying master protocol designs were highlighted.

However, master protocol designs are not without risk since these study designs often require considerable investment, more sophisticated governance, and complex analysis. The risk-benefit profile is unique to each study and must clearly articulate

Definition	Description	Reference
Master Protocol Study	***A single overarching design developed to evaluate multiple hypotheses***, and the general goals are to improve efficiency and establish uniformity through standardisation of procedures in the development and evaluation of different interventions. ***Under a common infrastructure, the master protocol may be differentiated into multiple parallel substudies*** to include standardised study operational structures, patient recruitment and selection, data collection, analysis, and management	EU-PEARL (1) Park et al 2019
Protocol Scaffold	***A visual aid to help plan for how the protocol content will be distributed between the core and subprotocols.*** A protocol scaffold is most easily presented by extracting the protocol template's table of contents and indicating whether content is located in the core versus subprotocols, whether content is repeated, or whether content is complementary	N/A
Core Protocol (document)	***Protocol document describing content for the overarching study design that is applicable to all substudies.*** Common content examples include a general introduction to the master protocol study, common objectives and endpoints/estimands, rationale for conducting the master protocol study, and common administrative, regulatory, and operational elements. ***Also referred to as "master protocol"***	
Subprotocol (document)	***Protocol document or content that is specific to an individual substudy.*** Synonyms include "intervention specific appendices", "domain specific appendices", "study modules", and "comparison protocols"	

Table 1: Terminology

the benefits and risks of employing a master protocol design over conventional designs. Performing a proportionate risk-benefit assessment at the start allows all stakeholders to enter the protocol development stage knowing the strengths and weaknesses of the proposed approach and set the foundation for risk-based quality management.

Scientifically Sound Rationale for the Master Protocol Design and the Shared Scientific Framework

A sound design rationale can take many forms and will depend on the participant population(s), study intervention(s), and the risk-benefit assessment. Collectively, any currently planned and anticipated future substudies must obey this rationale in that they need to meet the justification for the shared scientific framework.

This must be established pre-protocol as it precedes protocol structure discussion and may require a study design rethink if the task cannot be achieved. If, for example, the study team are looking to combine two studies into one just to avoid the operational burden of setting up two separate studies, then addressing the rationale for the shared scientific framework may highlight that a design rethink is required. Such a rethink is more beneficial at the beginning, rather than during, protocol development.

Clear Protocol Structure and Submission Approach

Over the last decade, the adoption of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and the TransCelerate Biopharma Common Protocol Template have served to harmonise industry protocols around a common structural framework (10, 11). This work has been crucial for not only defining common protocol components but also bringing order and clarity to conventional protocols. Regarding master protocol design terminology, the common understanding is that a master protocol study consists of a master protocol in combination with substudies. When referring to the different protocol parts for these, terminology is not as clear. To avoid conflating protocol structure with master protocol design discussion, the core protocol can be considered as the protocol document that describes content for the overarching study design that is applicable to all substudies (**Table 1**).

Similarly, for each substudy, subprotocol can be used when discussing protocol content, appendices, or independent document content that is specific to an individual substudy.

When looking at how content is distributed between core and subprotocols, we're now starting to see common master protocol structures emerging (12). Although it is unlikely that a single protocol template can span the range of basket, umbrella, and platform configurations, there is promise on the horizon for platform designs with the pending release of EU-PEARL's platform template that's scheduled for later in 2023 (13). Once the master protocol has been

developed, it forms part of the submission documentation that needs to be submitted to the regulatory authorities where the intended study is to take place. Master protocol design submission strategies similarly suffer from difficulties in adapting the conventional process to master protocols.

Current guidance from the FDA and EMA indicates that master protocol designs can be submitted under a single registration number or independently as separate subprotocols (1, 14, 15).
This guidance, although helpful, does not provide the granular detail to actually register and submit a master protocol study to each regulator. This leads to each study team needing to overcome this obstacle each time a master protocol study is developed.

Thankfully, like templates this too is changing as recent research from the National Institutes of Health has provided some welcomed and detailed guidance on the submission and reporting strategy for the USA (16).

Additional Schematics to Describe the Study Design Aspects and Overall Study Schedule

Protocol schemas are frequently undervalued as communication tools despite being the cornerstone for readers to get an overview for what the study structure looks like.

For master protocol studies, there is a need for schema to convey the

> Master protocol studies are shown to be a sustainable and economically viable approach to clinical study evaluation

structure of the study and to convey the structure of the protocol.

When the protocol is live, readers will need to be able to pick up the protocol and navigate its content quickly – the protocol schema can help them do this.

For starting a protocol – if the schemas are already in good shape to begin with, this increases the likelihood that all stakeholders participating in protocol development will be aligned in their understanding of the study design and structure of the protocol.

Detailed Communication Plan Linked to the Overall Study Schedule, Describing for Example, the Start and Termination of Subprotocols or Treatment Arms

In this context, a communication plan refers to the plan by which all stakeholders (e.g., investigators, regulatory authorities, ethics committees, etc.) are informed of the opening and closing of subprotocols, any safety signals, and subprotocol results – including any interim results or results from early termination.

The study governance/leadership structure, master protocol design, and number of countries/sites will be key information that will influence how such a communication plan would look.

Developing the basis for this communication plan prior to committing time and effort to the protocol development stage will help clarify expectations and assumptions that may influence protocol content as its being developed.

How Research Questions, Objectives, and Endpoints Apply to Specific or Across Subprotocols in a Study

Within the overarching master protocol study framework, research questions, objectives, and endpoints may be applied unevenly between the substudies. Common objectives and endpoints may form part of the shared scientific framework or lend themselves to circumstances where data can be shared or borrowed between substudies. Recent work by Collignon *et al* sought to address estimands for master protocols and highlight other common statistical challenges such as type I error control, design characteristics such as non-concurrent controls and changing randomisation/ allocation ratios, and bias/external validity (17).

As for other sections, having a clear understanding of how the shared elements will be distributed will help align stakeholders on shared versus individual elements before getting into the granular detail of the protocol.

Preparing to Write the Protocol

Using a Protocol Scaffold to Map Content

Once the outline establishes the study framework and limits, the protocol needs to be built based on these elements.

A protocol scaffold is a visual aid to help map how the protocol content will be distributed between the core and subprotocols, and is most easily presented by extracting the protocol template's table of contents and indicating whether content is located in the core versus subprotocols, and whether content is complementary (**Table 1**).

The visual approach of using a protocol scaffold helps to communicate with all team members and make sure that the stakeholders have an understanding and expectation of what they will receive as the first draft of the protocol.

An added benefit is that this can also be used to test the assumptions for the protocol structure and reconfirm the selected protocol structure is optimal for the study design when considering all components of the document.

Setting Timelines to Accommodate Writing and Reviewing Tasks

One substantial differentiation from other study designs is that most master protocol study protocols have a greater volume of content that needs to be generated, interlinked, and reviewed.

This places greater demand on protocol authors and reviewers. Using staggered or extended timelines that spread the reviewing workload over a more manageable timeframe (i.e., either reviewing different parts in sequence or increasing the overall reviewing time) can aid reviewers in successfully completing the review task within the allocated time (12). The risk of not doing so is that either that the timelines cannot be upheld and require shifting or that team members do an incomplete review.

For the former, shifting timelines are not only an inconvenience to the study team but also are an inefficient use of time as other commitments that were built around the timelines need to be adjusted for (i.e., a two-day delay at the

beginning can easily add weeks to the end of the timelines as adjustments are made).

For the latter, an incomplete review increases the risk of crucial items or questions being missed – this can easily derail protocol development if identified at a late stage of development or, worse still, require costly amendments soon after a protocol is live.

Managing Content During Protocol Reviews

Conventional protocols consist of a design and population backbone where the overall objectives and study framework (design) are paired with increasingly patient-centric population requirements (eligibility criteria, lifestyle considerations, flexibility etc.).

With master protocol designs, the content split between core and subprotocols brings in additional complexity as related content is divided between core and subprotocol sections.

Careful implementation of content using a protocol scaffold is a good starting point for protocol development, however, maintaining the content relations as reviewers provide input during the protocol development lifecycle requires careful management to avoid comments being lost, reviewers contradicting each other, or logic loops being incorporated (where one section refers to another and the other section refers back to the first).

Giving reviewers some training on how to approach the content will mitigate the impact of these circumstances occurring. For example, if content is shared between the core and subprotocols and the protocol spans hundreds of pages, targeted review of specific content and locking previously approved content may help reviewers to avoid duplicating work and needing substantial time to achieve their goal.

Concluding Remarks

Master protocol studies are shown to be a sustainable and economically viable approach to clinical study evaluation. Additional activities for developing the study design outline and preparing for protocol development are needed to prospectively build quality into the master protocol study.

Early engagement between authors and all team members to address the tasks outlined above will help establish a solid foundation for protocol development.

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The Lay Protocol Synopsis – What and How?

Is the protocol synopsis in lay language recommended by the new regulation feasible and fit for purpose?

Lisa Chamberlain James at Trilogy Writing & Consulting Ltd

In 2014, the EU introduced a new regulation: EU CTR 536/2014 (1). This regulation replaced the previous Clinical Trials Directive 2001/20/EC, and became mandatory with the opening of the Clinical Trials Information System (CTIS) on 31st January 2022 (2). The EU CTR applies to all investigational medicinal product studies (currently, medical devices are not included) that take place in at least one EU or European Economic Area member state, and by the end of January 2025, all studies must be transferred to CTIS. The new regulation was introduced to ensure that the rules for the assessment of clinical study applications and the conduct of clinical studies were identical throughout the EU.

There were many new aspects introduced by the regulation, but two new requirements have arguably caused most of the discussion: the requirement for a *Lay Summary of Clinical Trial Results*, and a recommendation for a *Protocol Synopsis in lay language*. One can speculate that these new requirements were driven by the frustration that almost 20% of clinical studies conducted in the EU do not report their results even in a register, and as part of the EMA's drive towards transparency and openness (3). But whatever the reason for their genesis, they have caused much discussion in the industry, because they call upon (and in fact necessitate) a completely different writing skill set aimed at a completely different target audience.

For the first time, companies are required to use information given in regulatory documents and produce summaries for the general public. This entails explaining complex scientific and clinical information clearly, concisely, without being biased or promotional in any way, and in a way that is also understandable to someone with no specialist scientific or technical knowledge.

The content requirements of the lay summary of clinical trial results are outlined in full in Annex V of the Regulation. However, in contrast, the protocol synopsis is only mentioned in one line in Annex 1 (D.24), which states simply, 'the protocol shall be accompanied by a synopsis of the protocol'.

Understandably, a request for more guidance and explanation was made, and more detail of the protocol synopsis content requirements was given as part of the EMA's 'Question & Answer' document (version 6.2), which was issued in September 2022 (4). These protocol synopsis requirements are extensive and include a maximum page allowance.

This article will look at the requirements for the protocol synopsis (with a particular emphasis on how this relates to the recommendation for a protocol synopsis in lay language) and discuss if it is feasible to produce a fit for purpose document as required.

Requirements and Challenges of the Protocol Synopsis

The Protocol Synopsis is a summary of the main aspects of the protocol, and there is a recommendation from the Authority to produce a version in language that is 'understandable to a layperson'. The latest guidance does not define, describe, or state what a 'layperson' is, but Version 2 of the Recommendations of the expert group on clinical trials for the implementation of regulation (EU) No 536/2014 stated that information for laypersons should 'not assume any prior knowledge of the trial, of medical terminology or clinical research in general' (5). Therefore, all of the challenges of

writing for this audience, including consideration of health literacy and health numeracy levels etc., must be kept in mind when writing for a lay audience (6, 7, 8). In this article, I will focus on the specific challenges associated with the protocol synopsis requirements as set by the authority.

Sections of the Protocol Synopsis

The guidance outlines nine sections that should be included in the Protocol synopsis, and helpfully offers some description for each. Below, I've highlighted each of the nine sections and discussed specific challenges for plain language writing (4):

1. EU trial number and full trial title. Study titles can often not only be extremely lengthy (a paragraph is not unusual), but also contain very complex concepts of study design. This is very confusing and off-putting for the reader and would require explanation and simplification.

2. Rationale: Specify background and hypothesis of the trial. There is no guidance on how much background should be given in Section 2, which suggests that an extensive background could be given. There is no guidance on which aspects of the background should be the focus of this section.

3. Objective: Specify the main and secondary objectives of the trial. The guidance does not state which of the main and secondary objectives should be included in this section. Whilst it would be reasonable to include all of the main objectives, there may be a considerable number of secondary objectives; in which case some element of judgement is called for. A consideration should be made of the patient's view in this – sometimes objectives that are most relevant for the sponsor or for the drug under investigation are not the most pressing for the patient. This can lead to a complex decision-making process during protocol synopsis writing.

4. Main trial endpoints: Describe the main trial endpoints and when they are assessed, e.g., the main trial endpoint is the percent change in the number of events from baseline to a specified time or the total number of adverse reactions at a particular time after baseline.

5. Secondary trial endpoints: Describe the secondary trial endpoints, and when they are assessed e.g. number of adverse events until 30 days post end of treatment. The main and secondary study endpoints (Sections 4 and 5) can be very complex and take a large amount of space to explain in plain language. The guidance also suggests that all secondary endpoints should be included, which could be a considerable number depending on the study, a problem that is compounded by the requirement to not only describe but state the timeframe of the assessments.

6. Trial design: Describe the design and the expected duration of the trial for the individual subjects, e.g., double-blind placebo controlled clinical trial where subjects are participating for X weeks. Clinical study designs can be very complex, involving crossovers, washout periods, randomisation etc. These concepts must be simplified and explained if the layperson is to understand their meaning. Additionally, the study design and population (Sections 6 and 7) are often most easily explained using infographics, which can work very well but do take up a lot of space.

7.Trial population: Describe the trial population, indicating the main inclusion criteria including age and disease/healthy volunteer and the main exclusion criteria to protect the subject, e.g., patients with moderate asthma 18-55 years with normal kidney and liver function and without gastrointestinal ulcer or risk factors for a cardiac arrhythmia; healthy volunteers 18-60 years not exposed to X-Ray examinations during the last 12 months. Section 7 requires a description of eligibility criteria, another section – like Sections 4 and 5 – that can be extensive and involve a lot of complicated clinical and technical terms. A description of the eligibility criteria in clinical regulatory language often takes a page alone (and we must consider that extra words are often necessary to explain concepts in plain language).

8. Interventions: Describe interventions and treatment duration, also including background treatment if any, e.g., one group receives a 10mg tablet of product X twice daily for Z weeks while also receiving product Y as background treatment and the other group receives a placebo tablet twice daily as well as product Y. Also describe trial-related diagnostic and monitoring procedures used. The requirement to include a description of the background treatment and study related diagnostic and monitoring procedures could be extremely lengthy on their own, depending on the therapy area. But for a layperson to understand them and their implications, a large amount of explanation in plain language is needed to describe what was done.

9. Ethical considerations relating to the clinical trial, including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risks. A benefit-risk analysis should be done for the trial-specific treatments and interventions, clearly explaining if the trial involves an expected individual benefit (e.g., as required in emergency situations) or a group benefit. When a trial is placebo-controlled, a brief justification should be given. If a non-therapeutic trial is carried out in vulnerable groups, e.g., in minors, incapacitated persons, pregnant or breastfeeding women, their inclusion has to be justified and it should be explained why the risks and burden are considered minimal and why the trial can only be performed in this particular patient group. The

trial-specific risks and burdens for subjects and caregivers (if applicable) related to diagnostic, therapeutic, and monitoring procedures should be justified, e.g., the amount and number of blood samples, the number of site visits, physical examinations or other tests, as well as physical and physiological discomfort associated with trial participation. An ethical discussion and a benefit-risk analysis is extremely challenging to condense into a meaningful, plain language document. Explaining benefits and harms to a layperson is one of the most challenging aspects of this work, and requires not only highly honed medical writing skill, but also an appreciation of cultural sensitivities and an awareness of tone.

Finally, unlike the lay summary of clinical trial results, the protocol synopsis has a required maximum page limit of two pages. Considering all of the challenges outlined above and that it generally takes more words (and therefore space) to explain complex concepts in plain language, the two page limit would make a fit for purpose document (either in plain language or not) almost impossible to achieve for all but the most simple studies.

A Path Forward?

A fit for purpose protocol synopsis covering all of the mandated sections in the level of detail required, either in plain language or not, is a herculean task to achieve in two pages; a task that in many cases will be impossible to achieve. This is a great shame (and cause of much frustration) because arguably the need for a plain language protocol synopsis grows with the increasing complexity of the study in question.

Some companies have decided that the recommendation can be overlooked, and some are exploring the use of a glossary to allow them to step around the two-page limit by adding explanations of terms and abbreviations to a separate document.

Unfortunately, this not only risks uncoupling the glossary from the main text, but also requires the reader to do quite a lot of memory work and cross referencing to be able to understand the document – a big ask for all but the most dedicated of readers.

Nevertheless, despite the challenges, a plain language version of the study protocol is a welcome addition for patients and the general public as it provides a big step forward for transparency of the whole clinical development process. Despite the current operational limitations, the concept is sound – providing a simplified, easy to understand summary of how and why a study was done for the public is needed and necessary.

As structured content becomes more prevalent in industry, in the future text used in the informed consent form could easily be carried through to the lay summary of clinical trial results to ensure consistent messaging for patients, which would increase understanding, and reduce effort for medical writers.

In the short-term, with ongoing dialogue and feedback between sponsors and the authority, I envisage (and hope) for a relaxation of the two-page limit. Given that medical writers, and particularly writers working in the plain language area strive to produce the most concise documents possible for the public, a suggested size rather than a required size would allow medical writers to produce clear, understandable, fit for purpose documents that are as short as possible. Surely this is the ultimate aim for all parties involved.

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