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Analysis and Optimization of the Comprehensibility and Relevance of Risk Communication in Patient Information (SIS/ICFs) for Clinical Trials.

verfasst von | submitted by

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Abstract:

Background: Subject Information Sheets/ Informed Consent Forms (SIS/ICFs) are essential for ethical clinical research but are frequently criticized for excessive length, complex language, and unclear risk communication. Regulatory changes, like the EU General Data Protection Regulation (GDPR), as well as developments in novel testing methods (e.g., genetic testing, biomarkers), may further impact the structure, content, and readability of SIS/ICFs, including considerations related to biobanking.

Objectives: This thesis analyzes structural and content-related characteristics of German-language SIS/ICFs, focusing on risk–benefit communication, data protection, and biobanking. The study addressed two main questions: 1. How do SIS/ICFs differ between early-phase (I/II) and late-phase (III) clinical trials? 2. How have SIS/ICFs evolved before and after GDPR enforcement?

Methods: A retrospective text analysis of 67 SIS/ICFs from 56 clinical trials was conducted. Experiment 1 compared Phase I/II (n = 19) and Phase III (n = 24) SIS/ICFs. Experiment 2 examined temporal changes using 24 Phase III SIS/ICFs (2011–2014 vs. 2022–2024). Quantitative metrics (page, word count, etc.) and qualitative coding (risk–benefit framing, data protection, biobanking content, etc.) were evaluated based on predefined coding matrices.

Results: The analysis for experiment 1 revealed distinct structural trends shaped more by regulatory frameworks than by trial phase. No significant difference in total length or risk-section size was observed between Phase 1/2 and Phase 3 SIS/ICFs (31.5 vs. 33.2 pages; $p > 0.5$), although Phase 3 documents more frequently included concluding risk–benefit balance sections (20.8% vs. 5.3%). A positive correlation between the number of participating countries and SIS/ICF length was evident in Phase 1/2 trials ($p = 0.026$), but not in Phase 3. Post-GDPR SIS/ICFs of Experiment 2 were markedly longer (+18 pages, +4,874 words; $p < 0.0001$), with expanded data protection content (+643 words; $p = 0.0062$) and a significant rise in explicit GDPR references ($p = 0.0458$). The biobanking word count increased both in absolute length (240 vs. 544 words; $p = 0.0151$) and overall complexity, while „visual elements“, though associated with longer documents, remained limited to 21% of SIS/ICFs from Experiment 2.

Conclusion: Our findings demonstrate that regulatory changes, particularly GDPR, have a more profound impact on SIS/ICF length and complexity than trial phase. While increasing use of common templates and regulatory guidance appears to have promoted a more uniform organization of SIS/ICFs (structural harmonization), national regulatory requirements and ethics committee guidelines still lead to notable differences in document structure and level of detail, particularly in data protection and risk sections. While risk communication remains a critical component, it is often overshadowed by legal and procedural content, with fewer than one quarter of SIS/ICFs providing an explicit risk–benefit synthesis. The post-GDPR increase in content does not necessarily improve participant comprehension and may instead exacerbate information overload. Visual elements and structured summaries, though still underused, offer potential pathways to better readability. To achieve meaningful informed consent, SIS/ICFs must move towards concise, modular designs that integrate clear risk–benefit framing, standardized data protection language, and targeted visual aids. These strategies would balance regulatory compliance with the ethical imperative of patient understanding. The concept of Cumulative Risk Exposure (KRE) (Idea by Eva Maria Zebedin-Brandl), introduced in this thesis, represents a novel approach to quantify the aggregated ethical burden of clinical risks across participants. KRE could theoretically complement traditional risk–benefit assessments by capturing the population-level impact of adverse events. Future studies could test its feasibility and acceptance among regulators and ethics committees.

Zusammenfassung:

Hintergrund: Probandeninformationen und Einwilligungsformulare (SIS/ICFs) sind für die ethische Durchführung klinischer Studien unerlässlich, werden jedoch häufig wegen übermäßiger Länge, komplexer Sprache und unklarer Risikokommunikation kritisiert. Regulatorische Änderungen, wie die EU-Datenschutz-Grundverordnung (DSGVO), sowie wissenschaftliche Fortschritte, etwa durch neue Test- und Analysemethoden, können die Struktur, den Inhalt und die Verständlichkeit von SIS/ICFs zusätzlich beeinflussen, einschließlich der damit verbundenen Aspekte wie Biobanking.

Ziele: Diese Arbeit analysiert die strukturellen und inhaltlichen Merkmale deutschsprachiger SIS/ICFs mit Schwerpunkt auf Risiko-Nutzen-Kommunikation, Datenschutz und Biobanking. Es wurden zwei zentrale Fragen untersucht: 1. Wie unterscheiden sich SIS/ICFs zwischen frühen Studienphasen (I/II) und späten Studienphasen (III)? 2. Wie haben sich SIS/ICFs vor und nach Inkrafttreten der GDPR entwickelt?

Methoden: Es wurde eine retrospektive Textanalyse von 67 SIS/ICFs aus 56 klinischen Studien durchgeführt. Experiment 1 verglich Phase I/II (n = 19) mit Phase III (n = 24) SIS/ICFs. Experiment 2 untersuchte zeitliche Veränderungen anhand von 24 Phase III SIS/ICFs (2011–2014 vs. 2022–2024). Quantitative Metriken (Seiten-, Wort-zahl, etc.) und qualitative Kodierungen (Risiko-Nutzen-Darstellung, Datenschutz, Biobanking-Inhalte etc.) wurden anhand vordefinierter Kodiermatrizen bewertet.

Ergebnisse: Die Analyse der SIS/ICFs in Experiment 1 zeigte klare Strukturtrends, die stärker durch regulatorische Rahmenbedingungen als durch die Studienphase geprägt sind. Es gab keinen signifikanten Unterschied in der Gesamtlänge oder im Umfang der Risikosektion zwischen Phase I/II und Phase III SIS/ICFs (31,5 vs. 33,2 Seiten; $p > 0,5$), jedoch enthielten Phase III-Dokumente häufiger Risiko-Nutzen-Bewertungen (20,8 % vs. 5,3 %). In Phase I/II-Studien zeigte sich eine positive Korrelation zwischen der Anzahl teilnehmender Länder und der Länge der SIS/ICFs ($p = 0,026$), in Phase III hingegen nicht. Die Analyse von Experiment 2 ergab das SIS/ICFs nach Inkrafttreten der GDPR deutlich länger ($p < 0,0001$) waren, sowie erweiterten Datenschutzinhalt ($p = 0,0062$) und eine Zunahme expliziter GDPR-Verweise ($p = 0,0458$) aufwiesen. Der Gesamtumfang der Biobanking-Abschnitte nahm absolut (240 vs. 544 Wörter; $p = 0,0151$) und auch in der allgemeinen Komplexität zu. Visuelle Elemente, obwohl sie mit längeren Dokumenten assoziiert waren, blieben auf 21 % der SIS/ICFs aus Experiment 2 beschränkt.

Diskussion: Die Ergebnisse zeigen, dass regulatorische Änderungen, insbesondere die GDPR, einen stärkeren Einfluss auf Länge und Komplexität von SIS/ICFs haben als die Studienphase. Während die zunehmende Nutzung gemeinsamer Vorlagen und regulatorischer Leitlinien (strukturelle Harmonisierung) vermutlich zu einer einheitlicheren Gliederung von SIS/ICFs beigetragen hat, bestehen durch nationale regulatorische Anforderungen und Vorgaben der Ethikkommissionen weiterhin deutliche Unterschiede im Dokumentaufbau und im Detaillierungsgrad, insbesondere in den Abschnitten zu Datenschutz und Risiken. Risikokommunikation bleibt ein zentrales Element, wird jedoch oft durch rechtliche und prozedurale Inhalte überlagert, wobei weniger als ein Viertel der SIS/ICFs eine explizite Risiko-Nutzen-Gegenüberstellung liefert. Visuelle Elemente und strukturierte Vergleiche, die bisher wenig genutzt werden, könnten die Lesbarkeit verbessern. Um eine informierte Einwilligung zu erreichen, sollten SIS/ICFs kürzer und modular aufgebaut werden, mit klarer Risiko-Nutzen-Darstellung, standardisierter Datenschutzsprache und gezielten visuellen Hilfsmitteln. Das in dieser Arbeit eingeführte Konzept der Kumulativen Risikoexposition (KRE) (Konzept von Eva Maria Zebedin-Brandl) stellt einen neuartigen Ansatz dar, um die aggregierte ethische Belastung klinischer Risiken über alle Teilnehmenden hinweg zu quantifizieren und so die klassische Risiko-Nutzen-Abwägung ergänzen. Zukünftige Studien könnten die Anwendbarkeit und Akzeptanz dieses Ansatzes bei Behörden und Ethikkommissionen prüfen.

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1. Introduction

1.1. Background

1.1.1. Clinical Research and the Importance of Informed Consent:

Clinical drug development is a complex and highly regulated process that serves as the backbone of evidence-based medicine. At its core, this process includes the conduct of clinical trials, systematically planned studies in human participants designed to evaluate the efficacy, safety, and tolerability of investigational medicinal products. These trials are typically structured across multiple phases, ranging from early-phase studies focused on pharmacokinetics and dose-finding to large-scale confirmatory phase III trials, which typically aim to compare investigational products with standard therapies.

In the context of oncological research, clinical trials often involve novel, advanced, and experimental high-risk therapies, posing particular ethical and communicative challenges. Participants frequently face life-threatening diagnoses and complex treatment options, which makes transparent, comprehensible information especially critical. (1)

Informed consent is a process in which a person voluntarily agrees to participate in a procedure, treatment, or research study after receiving all relevant information. In medical, legal, and research contexts, informed consent ensures that individuals make educated decisions about their bodies, rights, and participation in activities that may affect them. To be truly effective, this process must address both the quality of the information provided and the dynamics between those who provide and those who receive it. Shou et al. (2024) emphasize that participants often find full comprehension of consent materials challenging or unattainable, and that trust and clear, interactive communication with clinicians play a decisive role in enabling informed decision-making. They further note that emotional distress during the consent process can negatively affect participants' ability to evaluate risks and benefits objectively, highlighting the need for communication strategies that reduce both cognitive and emotional burdens. (2)

Patient-centered barriers, such as education level, illness severity, the psychological response to the disease, and process-centered factors, including the readability and length of consent forms and the timing of discussions, can significantly affect a participant's ability to provide truly informed consent (Taylor, 1999). Addressing these barriers requires not only document optimization but also a communication approach that allows for sufficient time, interaction, and clarification. (3)

The consent process is inherently shaped by a power imbalance between doctor and patient and between institution and individual (Bowman et al., 2012). The same is true for the relationship between researchers and participants. Recognizing this asymmetry is essential to building mutual trust and ensuring that consent becomes a meaningful exercise of autonomy rather than a mere legal formality. (4)

Medical professionals should realize that valid consent does not require the participant to understand every detail of a proposed intervention. Millum and Bromwich (2018) defined three essential consent components: 1. knowing that they are providing consent, 2. understanding how to exercise their right to give or refuse consent, and 3. being aware of what exactly they are consenting to. Clear and effective communication between researcher and participant is thus crucial for transforming consent from a bureaucratic requirement into an ethically sound interaction. (5)

Informed consent must be regarded as a dynamic process grounded in autonomy and self-determination. Overly complex or legalistic SIS/ICFs risk reducing participants to passive signatories, thereby undermining the very autonomy that forms the ethical foundation of clinical research (McCabe, 1999). (6)

Furthermore, informed consent alone is not sufficient to make clinical research ethical. A comprehensive ethical framework also requires factors such as a favorable risk-benefit ratio, scientific validity, fair subject selection, and ongoing respect for participants (Emanuel et al., 2000). This broader view provides a bridge to the international ethical codes and regulatory frameworks that shape modern clinical research. (7)

Building on these ethical foundations, contemporary approaches such as Shared Decision Making (SDM) extend the traditional notion of informed consent by emphasizing an interactive process. As Charles et al. (1997) highlight, SDM requires at least two active participants (patient and clinician) who share information, deliberate on treatment options, and jointly agree on a course of action. This approach addresses the informational and power asymmetries described by Bowman et al. (2012), turning consent from a one-way transfer of information into a collaborative dialogue that aligns with patients' values and preferences. (4,8)

1.1.2. Regulatory and Ethical Foundations and Legislation:

Conducting clinical trials ethically and legally requires adherence to a variety of international frameworks. To achieve an acceptable amount of conscious agreement, many international template documents are available. While this study focuses on European and Austrian contexts, foundational principles are drawn from globally recognized ethical codes, most notably, the Nuremberg Code (1947), the Declaration of Helsinki (1964), and the Belmont Report (1979). (9–11)

Modern ethical foundations of informed consent trace back to these foundational documents, which provide detailed guidance on informed consent, risk-benefit assessment, and protection of research subjects. While not directly incorporated into Austrian law, their content is widely recognized as an ethical standard for clinical research. The goal of such documents is to prevent ethical failures in medical research and ensure the protection, dignity, and rights of human subjects. Both the Nuremberg Code and the Declaration of Helsinki were created as direct responses to unethical medical experiments and atrocities committed by "trained" medical personnel, also during World War II and other unethical research practices in the mid-20th century.

The Declaration of Helsinki (Section 26) provides further clarity on how informed consent should be communicated, emphasizing the importance of using clear language and ensuring participants' right to withdraw at any time. The declaration states: "In medical research involving human participants capable of giving informed consent, each potential participant must be adequately informed in plain language of the aims, methods, anticipated benefits and potential risks and burdens, qualifications of the researcher, sources of funding, any potential conflicts of interest, provisions to protect privacy and confidentiality, incentives for participants, provisions for treating and/or compensating participants who are harmed as a consequence of participation, and any other relevant aspects of the research.

The potential participant must be informed of the right to refuse to participate in the research or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information and communication needs of individual potential participants as well as to the methods used to deliver the information.

After ensuring that the potential participant has understood the information, the physician or another qualified individual must then seek the potential participant's freely given informed consent, formally documented on paper or electronically. If the consent cannot be expressed on paper or electronically, the non-written consent must be formally witnessed and documented."

(Declaration of Helsinki, Section 26) (10)

The ethical principle of "respect for persons" in the Belmont Report (1979) establishes the normative foundation for informed consent, emphasizing autonomy and comprehension. The Capability Approach developed by Amartya Sen and Martha Nussbaum provides a complementary perspective by operationalizing this principle: rights only become meaningful if individuals possess the real capability to exercise them. In the context of clinical research, this means that informed consent must go beyond formal disclosure requirements and actively ensure that participants have the substantive ability to understand and decide. (Sen, 1999; Nussbaum, 2011) (12–15)

As Sen highlights, rights and resources alone are insufficient: only the real capability to transform them into valued functionings constitutes genuine freedom. Applied to informed consent, this means that access to documents is inadequate unless participants are also given the real opportunity to comprehend and act upon them. (15) As Nussbaum (2003) argues, rights are not effectively secured simply by being recognized on paper; they are realized only when individuals are made truly capable of exercising them. (14)

The legal framework governing informed consent for clinical trials within the European Union is defined by EU Regulation No. 536/2014. This regulation applies to all clinical trials conducted within the European Union and harmonizes the rules for the conduct of clinical trials across member states, including Austria. Specifically, Articles 28 and 29 describe the requirements for obtaining informed consent. Informed consent must be voluntary, informed, and given in writing after the subject has been fully informed about the trial's nature, objectives, risks, and benefits. (16,17)

At the European level, over the past decade, clinical trials have faced increasing regulatory complexity, particularly following the implementation of the General Data Protection Regulation (GDPR) in 2018 and the EU Clinical Trials Regulation (EU CTR 536/2014) with the associated Clinical Trials Information System (CTIS) in January 2022. These regulations mandate extensive disclosures regarding data handling and privacy, which may have unintended consequences on the length and readability of SIS/ICFs. (16,18)

The General Data Protection Regulation (GDPR, Regulation (EU) 2016/679), applicable since May 2018, profoundly reshaped the legal framework for clinical research in the European Union. Its guiding principles, lawfulness, fairness, transparency, data minimization, and accountability (Art. 5), require sponsors and investigators to justify, document, and communicate many aspects of personal data processing. Given that health data, along with other types such as genetic, biometric, or data concerning sex life or sexual orientation, is classified as "special categories of personal data" (Art. 9), their use in clinical trials is permissible only under strict safeguards. Informed consent under the GDPR must be freely given, specific, informed, and revocable (Art. 6–7), thereby reinforcing the ethical imperative of autonomy while simultaneously introducing additional legal complexity. Furthermore, transparency obligations (Art. 12–14) mandate that participants are explicitly informed about their rights, including access, rectification, erasure ("right to be forgotten"), restriction of processing, data portability, and the right to object (Art. 15–22). In practice, these requirements translate into extensive and highly technical sections within SIS/ICFs. While these clauses aim to strengthen participants' control over their data, they may have also contributed to considerable increases in document length and legal density, shifting the balance of information from risk–benefit communication toward legal compliance. (18)

Since 2023, clinical trial sponsors in the European Union must submit all new clinical trial applications in the Clinical Trials Information System (CTIS). National regulators in the EU Member States and EU/EEA countries also use CTIS. A single online application enables sponsors to apply for clinical trial authorization in up to 30 European countries.(19)

Clinical trials authorized under the previous legal framework (Directive 2001/20/EC) were registered in the EudraCT database, which served primarily as a trial registry without integrated extensive regulatory functions. Trials initiated before the full applicability of Regulation (EU) No. 536/2014 could continue to operate under this older framework until January 2025. As a result, many ongoing or completed trials, such as those included in this study, are still identified by their original EudraCT numbers. These legacy studies may later be transferred into CTIS as so-called "transition trials," but their EudraCT registration remains the primary reference for historical documentation and classification. (16,17,20–22)

For the purposes of this thesis, transition trials were explicitly excluded from the analysis. This decision was made to avoid interpretative ambiguity due to the dual regulatory nature of such trials. Therefore, the dataset includes only 1. trials still fully governed under the Directive and registered in EudraCT, and 2. newly authorized trials registered directly via CTIS under the Clinical Trials Regulation.

All trials included in this study are identified by their unique EU Clinical Trial Number (EUCT number) in the format YYYY-NNNNNN-CC-00. This format applies to both legacy trials registered in the EudraCT database (under Directive 2001/20/EC) and new trials submitted under Regulation (EU) No. 536/2014 via the CTIS platform. For consistency and comparability, this EUCT number was used as the primary identifier across the entire dataset.

EU Member States and EEA countries use the Clinical Trials Information System (CTIS) to carry out their legal responsibilities to assess and oversee clinical trials. Through CTIS, national regulators can collaboratively process clinical trial applications in more than one country, request further information, authorize or refuse a trial, oversee an authorized trial, and facilitate the expansion of trials to other EEA countries. This transparency also enables us to use the system for access to information in clinical trials conducted in the EEA through a searchable public website. Even though CTIS has introduced an unprecedented level of harmonization in the processing and oversight of clinical trial applications across EU/EEA countries, several aspects remain subject to discussion and decision at the national level. (19,23)

Modern-day clinical research must also adhere to Good Clinical Practice (GCP), as defined in the ICH Guideline E6(R2), which outlines the responsibilities of sponsors, investigators, and ethics committees, emphasizing participant protection, scientific integrity, and data reliability (ICH, 2023). (24)

In Austria, the national legal framework for clinical trials is defined by the Arzneimittelgesetz (AMG, 2025). It mandates approval by the Federal Office for Safety in Health Care (§ 28 AMG) and oversight by ethics committees, as well as clear written consent, explicit data protection agreements, and appropriate participant insurance (§§ 28–44 AMG). These requirements complement EU Regulation 536/2014 and ensure participant safety and rights. (25)

This study seeks to examine how effectively the scientific community continues to uphold these ethical standards in a way that benefits individual patients in clinical trials. Particular attention is given to the use of appropriate language structures and visual representations that convey essential information without overburdening the comprehension capacities of patients with diverse educational and cognitive backgrounds. In this study, such features were

operationalized via predefined coding matrices. For example, we coded the presence and type of visual elements (flow charts, cartoons/illustrations, tables) and summarized them in a display-element score (0–3). For language/structural features, we (e.g.) classified risk-likelihood wording (quantitative, qualitative, mixed), recorded whether a dedicated risk summary and any concluding risk–benefit statement were present, and noted the placement of the risk section as well as comparative framing vs. placebo or standard therapy.

A recent comparative analysis of informed consent regulations in six European countries (Bolcato et al., 2024) emphasizes that while written consent is generally required in many jurisdictions, some legal systems also accept oral consent in defined contexts, focusing on the quality of dialogue between patient and clinician rather than documentation alone. The authors also identify notable cross-country differences in how informed consent is legally defined, the scope it covers, and the level of detail it must contain, indicating an absence of complete harmonization. Furthermore, many legal systems include clear clauses that allow healthcare interventions without prior consent in emergencies or when patients are incapable of consenting, as long as strict legal safeguards are respected. (26)

Background Information regarding EudraCT- and EUCT-Number:

Each clinical trial in the EU is assigned a unique identifier with the format YYYY-NNNNNN-CC. 'YYYY' denotes the year of allocation, 'NNNNNN' is a six-digit sequential number, and 'CC' consists of check digits (European Commission, 2004). Under Directive 2001/20/EC, this identifier was referred to as the EudraCT number and served to identify a protocol throughout its lifespan (EMA, EU Clinical Trials Register Glossary). With the application of Regulation (EU) No. 536/2014 on 31 January 2022, new trials could already be submitted via the Clinical Trials Information System (CTIS). From 31 January 2023 onwards, use of CTIS became mandatory for all new clinical trial applications, which are assigned an EUCT number that retains the same format, while EudraCT numbers are retained exclusively for third-country files for trials conducted outside of the EU/EEA. No official EMA or Commission source reviewed in this thesis indicates a change in the numbering algorithm or frequency; the distinction may lie in the regulatory framework and the database in which the identifiers are managed. No departures from this structure have been noted in this thesis; all observable identifiers in CTIS continue to follow the YYYY-NNNNNN-CC pattern. The dataset analyzed in Experiment 2 of this study confirms that all EUCT numbers observed in CTIS retain the YYYY-NNNNNN-CC format. (16,20–22)

1.1.3. The Subject Information Sheet and Informed Consent Form (SIS/ICF) as Central Documents:

In this thesis, the term "ICF" (Informed Consent Form) is used to refer to both standalone ICFs and combined Subject Information Sheet/Informed Consent Form (SIS/ICF) documents. Informed consent forms are essential documents and a central component of the ethical framework in clinical research, serving both ethical and legal functions. Their primary function is to inform potential participants about the purpose, procedures, risks, benefits, and data protection policies associated with a clinical trial, thereby enabling autonomous and informed decision-making free from pressure and coercion. Beyond its ethical role, the informed consent form also has legal significance, as it constitutes a written, signed, and dated agreement between participant and investigator/sponsor, thereby establishing a binding framework for rights and obligations on both sides (ICH-GCP E6(R2), section 1.17, 1.28, 4.5.1) (24)

Despite its importance, empirical studies have repeatedly found that SIS/ICFs are often overly long, written in complex language, and poorly structured, a combination that impairs understanding, especially among individuals with limited health literacy. Furthermore, recent evidence points to a lack of standardization in how risks and benefits are communicated across different trial phases. Early-phase trials (Phase I/II) are often associated with greater uncertainty and higher risk, yet they do not consistently include detailed or comprehensible descriptions of risk likelihoods or mitigation strategies, as shown in work by Kahrass et al. (2020). (27)

Research on the informed consent process often aimed to gain data regarding understanding, recruitment/ participation rates, decision-making capacity, voluntariness, readability of consent documents, authorization, satisfaction, and institutional policies. (2,28–30) (e.g., specifically for antimicrobial trials: 2; broader overviews across trial types: 28–30).

In response, both regulatory guidance and researchers have called for improvements in language clarity, document structure, the inclusion of visual aids, and other innovative strategies like the validation and implementation of tools based on the use of artificial intelligence models. Current guidelines emphasize that SIS/ICFs should be written in plain language and organized logically, with special attention to critical information (ICH E6(R2), section 4.8). Where appropriate, they recommend the use of multimedia/visual formats (e.g., diagrams, images, or short videos) and comprehension checks. Authorities also recognize electronic informed consent and digital information leaflets (non-binding guidance). In parallel, recent studies show that many trial consent forms exceed average reading levels and that improving readability matters; for example, higher reading grade is associated with higher dropout, and AI–human workflows can reduce reading level while preserving medico-legal sufficiency (See Mirza et al. and Ali et al.). Despite these recommendations, challenges remain in achieving true comprehension among potential participants, particularly when it comes to complex topics such as biobanking, data protection, and risk disclosure. (24,28,31–35)

1.1.4. Risk Communication as a Central Challenge:

Effective risk communication is essential for enabling participants to make informed decisions, particularly in oncology trials, where investigational therapies often involve uncertain outcomes and potentially severe side effects. The way risks are framed (qualitatively (e.g., “rare”), quantitatively (e.g., percentages), or comparatively (e.g., versus standard therapy or placebo)) can heavily influence patient perception.

Prior research highlights that ambiguous or technical risk descriptors in informed consent documents are often used inconsistently, which may make it difficult for participants to accurately understand the likelihood of potential harms. (1,27) Early-phase trials (I/II), characterized by greater uncertainty, pose specific challenges in achieving balanced risk-benefit communication. (27) This thesis, therefore, places special emphasis on evaluating how risk–benefit information is structured, quantified, and communicated within SIS/ICFs.

Consistent with ICH E8(R1), early-phase ICFs should stress exploratory aims, surrogate measures, and greater risk-benefit uncertainty, whereas later-phase ICFs can anchor communication in clinically relevant confirmatory endpoints and a more mature safety profile. (36)

1.2. Objectives and Research Questions

This research employs a retrospective, descriptive, and quantitative text analysis design based on two experimental datasets of Subject Information Sheet and Informed Consent Forms (SIS/ICFs) by systematically investigating structural and content-related features in order to identify patterns in comprehensibility and relevance.

- **Experiment 1** compares SIS/ICFs from Phase I and Phase III trials, examining structure, length, thematic content, and internationalization.
- **Experiment 2** analyses Austrian SIS/ICFs from different time periods, investigating temporal trends, particularly before and after the implementation of the GDPR.

In addition to general comprehensibility and word count metrics, this study also explores two structurally and ethically critical content domains within SIS/ICFs: biobanking and data protection. Both topics are often embedded inconsistently within documents, lacking uniform headings, structure, or placement. Particularly in the case of biobanking, some SIS/ICFs include clearly labeled sections, whereas others either omit explicit references or scatter relevant content across multiple, unlabeled areas. This inconsistency complicates both participant comprehension and methodological evaluation. To enable a systematic and reproducible analysis, a structured framework was developed to classify data protection and biobanking-related content and to quantify word counts across several comprehensively defined complementary categories. These methodological frameworks allow for a more nuanced cross-document comparison and reveal considerable variation in how ethically critical information is communicated, highlighting the need for regulatory harmonization in SIS/ICF design. Across both experiments, such frameworks were operationalized via layered word-count schemes for complex sections like data protection, biobanking, and risk-communication to make heterogeneous ICFs comparable. (e.g., distinguishing dedicated sections, dispersed mentions, consent-element text, and cumulative totals). Definitions and allocation rules are detailed in Methods (Section 2.3, “Special Procedures for Complex Sections”).

Despite various descriptive studies on SIS/ICFs' length and structure, there is a lack of empirical work that systematically links document characteristics to trial phases, regulatory shifts (such as the GDPR), or structural themes such as biobanking and data protection.

Inadequate structure or excessive length in SIS/ICFs may hinder true informed consent, particularly among patients with limited health literacy, posing a threat to ethical research conduct. Findings from this study may inform future regulatory guidelines or sponsor practices, aiming for greater standardization and improved clarity in patient-facing trial documentation.

To address this aim, a set of predefined hypotheses was formulated and tested, as outlined in the Methods section.

1.2.1. Primary Objectives:

- Analyze the clarity, structure, and balance of risk communication within SIS/ICFs, with a focus on how risks and benefits are described across trial phases, time periods, and regulatory frameworks.
- Investigate how comprehensibility and relevance are influenced by trial characteristics such as phase, time period, regulatory shifts (e.g., GDPR), and study parameters like participant count and internationality.
- Assess the impact of these factors on overall document length, word count, and the treatment of key content areas, including data protection, risk communication, and biobanking.

1.2.2. Secondary Objectives:

- Assessing data protection and biobanking sections as complementary content domains
- Exploring the influence of study characteristics (e.g., number of countries, study phase) on the presentation of risks and benefits.

One of the study's additional objectives is to analyse the methods and tools used to present patient-relevant information effectively and to adapt it in a way that makes it understandable for individuals with varying levels of health literacy, intelligence, and education, thereby supporting the process of truly informed consent, which is a legal prerequisite for the lawful conduct of clinical trials.

1.2.3. Specific Focus: Risk Communication in Oncology Trials

Risk communication in oncology trials is particularly demanding. Experimental treatments often involve substantial uncertainties regarding adverse effects and therapeutic outcomes. Moreover, additional elements such as the use of placebo arms, the absence of standard-of-care options, or the long-term storage of biological samples further complicate the informational landscape.

It is within this context that the study investigates how selected oncology SIS/ICFs present and structure risk-related information. The study analyses variations in document length, content organization, use of visuals, and different types of consent forms. In doing so, it aims to assess how regulatory and ethical requirements translate into practice and where potential improvements in the design and delivery of informed consent materials may lie.

1.2.4. Research Questions and Hypotheses (Overview):

While detailed hypotheses are provided in the Methods section, the research is guided by the following overarching questions:

- How do SIS/ICFs differ in overall length, structure, and risk–benefit communication between early-phase (I/II) and late-phase (III) clinical trials?
- How have structural and content-related elements (e.g., data protection, biobanking) in SIS/ICs evolved before and after the enforcement of GDPR?
- What is the relationship between trial complexity (e.g., number of participating countries, presence of standard treatment or placebo arms) and the extent or structure of risk–benefit communication in SIS/ICFs?

1.3. Relevance and Outlook

By centering on the risk-communication challenge, this research contributes to the ongoing debate about how SIS/ICFs can be both comprehensive and understandable. The findings are intended to guide sponsors, regulators, and ethics committees toward clearer standards that align legal requirements with patient comprehension and autonomy.

Inadequate risk–benefit communication can lead to misunderstandings, biased decisions, or even trial withdrawal due to unmet expectations of the trial participant. Therefore, improving risk communication is not only a legal and ethical requirement but also central to patient autonomy and meaningful consent.

By examining structural and readability-related features that affect comprehension (e.g., sectioning and heading clarity, section length, jargon/technical terms/acronyms, and the placement/labeling of risk and data protection/GDPR content), this study provides insights that may inform both future regulatory guidelines and practical template improvements for SIS/ICFs. The expected contribution is twofold: 1. evidence on how regulatory shifts and document design affect patient-facing information, and 2. actionable guidance for sponsors, regulators, ethics committees, investigators, and medical writers to improve the quality of trial documentation.

In summary, this thesis investigates how SIS/ICFs present risks and benefits, with a focus on the interplay between document structure, readability-related aspects, and regulatory frameworks. Rather than measuring actual comprehension or applying formal readability scores, the analysis centers on content patterns and formal characteristics. As proxies, it uses length metrics (total and section-level word counts), structural features (presence/placement of dedicated sections and trial elements, use of lists/labels/visuals), and content markers (e.g., biobanking presence, proportion of GDPR-related text). Their interplay is explored descriptively through stratified comparisons (e.g., across trial phases and time periods (pre- vs. post-GDPR), and by study characteristics such as internationality and participant numbers), as detailed in the Methods section.

By analyzing variations across trial phases, time periods (particularly before and after GDPR), and study characteristics such as internationality and participant numbers, this study aims to identify patterns that influence patient comprehension and decision-making, along with recurring approaches and inconsistencies that may impact how patients perceive the information. Special attention is given to ethically critical domains, including data protection and biobanking, which are often inconsistently presented.

Through a systematic, retrospective text analysis of SIS/ICFs, this work highlights structural and language-related challenges that may hinder truly informed consent and derives recommendations for improving clarity and standardization. The findings are expected to contribute not only to academic discourse but also to practical guidance for sponsors, regulators, ethics committees, clinical trial investigators, and professionals drafting ICFs, aiming to enhance the quality of patient-facing trial documentation.

2. Methods

2.1. Study Design and Hypotheses

This thesis employed a retrospective, descriptive, and quantitative text analysis design to investigate the structure and content of informed consent forms (ICFs) used in clinical trials. The study is divided into two experiments:

- **Experiment 1** examines differences in ICFs between Phase 1/2 and Phase 3 clinical trials.
- **Experiment 2** explores temporal and regulatory influences, particularly before and after the implementation of the General Data Protection Regulation (GDPR) in 2018.

Both experiments share a common methodological foundation but include modifications tailored to the respective hypotheses. To ensure that the analyzed ICFs were evaluated against internationally recognized standards, the coding matrices were conceptually informed by key international and European guidelines (e.g., Declaration of Helsinki, ICH-GCP, EU Regulation No 536/2014), which specify essential information elements for participant information and consent. These guidelines were used as a reference framework to identify and define core content categories such as risk communication, data protection, and biobanking. For example, Section 26 of the Declaration of Helsinki emphasizes the need for a clear description of 'anticipated benefits and potential risks' in plain language. In line with this principle, the coding matrix included variables such as the presence, location, and word count of dedicated risk and benefit sections, as well as whether a summary of risk–benefit balance was provided. Similarly, ICH-GCP requirements on confidentiality and privacy (ICH E6(R2), Section 4.8) and the Regulation (EU) 2016/679 guided the inclusion of data protection variables, while EU Regulation 536/2014 informed the categorization of consent elements related to biobanking and data handling. The matrices were applied to a structured analysis of German-language ICFs retrieved from the **Clinical Trials Information System (CTIS)** and **Ethics Committee Registry of the Medical University of Vienna.** (10,16,18,19,24,36)

This study analyzed documents, sample templates, and requirements for informed consent forms (SIS/ICFs) sourced from international regulatory and ethical bodies, including the World Health Organization (**WHO**), the European Medicines Agency (**EMA**), the U.S. Food and Drug Administration (**FDA**), and the Strategic Initiative for Developing Capacity in Ethical Review **(SIDCER-FERCAP)**. National templates from **Austria** and **Germany** were also included. In addition, key international ethical guidelines such as the ICH-GCP Guidelines and the Declaration of Helsinki were examined. Relevant materials were identified through searches in databases including Google, PubMed, u:search, and Google Scholar. (10,24,36–46)

The review of these templates and guidelines served to identify recurring structural elements (e.g., risk–benefit description, confidentiality statements, withdrawal rights) and minimum content requirements that are considered ethically or legally essential. While the analysis was not the primary focus of this thesis, it highlighted, for example, that all international templates require a clear explanation of risks and benefits (Declaration of Helsinki, ICH-GCP, FDA Guidance), and that European templates often mandate a separate data protection section (EU 536/2014, GDPR). In addition to international guidelines, representative national templates for informed consent forms (ICFs) from Germany (Arbeitskreis Medizinischer Ethik-Kommissionen, AMG, Version 1.2, 2022) and Austria (MedUni Vienna Ethics Committee, Version 4.1, 2023) were reviewed. The purpose of this review was to identify key mandatory content elements and

structural features typically required by regulatory bodies. Both templates emphasize essential information such as risk–benefit communication, GDPR-compliant data protection, and withdrawal rights, while the German template provides more detailed guidance on biobanking and lay language. A summarized comparison of the key requirements is provided in Supplementary Table 8: Comparison of National and International Informed Consent Templates and Guidance Documents.

The overarching aim of this thesis was to analyze the clarity and balance of risk communication in informed consent forms (ICFs) used in clinical trials, with a particular focus on the comprehensibility, proportionality, and framing of risk–benefit information. In doing so, this study seeks to provide insights into underlying mechanisms that contribute to excessive length or complexity and to identify potential shortcomings of existing templates, which may be addressed in future research.

The primary objective of this study is to explore the themes related to the following hypotheses/ questions:

2.1.1. Experiment 1: Comparison by Trial Phase (Phase 1 vs. Phase 3)

- Scope note: All probabilities/likelihoods refer to how risk and benefit are reported in the SIS/ICF text (verbal descriptors or numerical frequencies). No study reports or outcome data were analysed. Trial characteristics (phase, multicentre/multinational, no. of countries) come from registry metadata.

Main Hypothesis:

H1: There is a significant difference in total word count and page count between SIS/ICFs for Phase 1 and Phase 3 clinical trials.

Secondary Hypotheses:

- H1a: SIS/ICFs for Phase 3 trials are longer (in word and page count) than those for Phase 1 trials.
- H1b: Risk communication sections (in word count and page count) are more extensive in Phase 1 SIS/ICFs than in Phase 3 SIS/ICFs.
- H1c: The ICF-reported likelihood of severe adverse effects is higher in Phase 1/2 than in Phase 3 trials.
- H1d: The ICF-reported likelihood of benefits is higher in Phase 3 than in Phase 1/2 trials.
- H1e: The overall number of countries involved in a clinical trial is positively associated with the word count and/or page count of the informed consent form.
- H1f: Multinational trials are more likely to include standardized or visual display elements compared to trials with a smaller overall number of countries involved.
- H1g: Phase 3 clinical trials are more likely to be multicentric, involving a higher number of countries, compared to Phase 1 trials.

2.1.2. Experiment 2: Temporal Comparison and Regulatory Influence

Main Hypothesis:

H2: SIS/ICFs released after the enforcement of the GDPR/ General Data Protection Regulation (2018) and after introduction of the CTR/ Clinical Trials Regulation are significantly longer and contain more extensive data protection information than those released before.

Secondary Hypotheses:

- H2a: SIS/ICFs released after the GDPR are more likely to contain explicit references like "right to erasure" or data retention duration, than those released before.
- H2b: SIS/ICFs released after the GDPR are more likely to include separate, dedicated data protection and biobanking consent forms and/ or additional box selection.
- H2c: Planned participant count is positively associated with the length of the risk communication section.
- H2d: The presence of biobanking content is positively associated with total ICF word count.
- H2e: SIS/ICFs that include biobanking content are more likely to have a higher number of additional separate signature forms.
- H2f: The level of detail in biobanking sections (e.g. storage duration, reuse scope, sample coding, …) correlates with the total word count of the ICF.
- H2g: The use of dedicated headings for biobanking content is associated with longer SIS/ICFs.
- H2h: SIS/ICFs after 2018 have a significantly higher Biobanking word count.
- H2i: Biobanking consent forms have become more common and (when present) more extensive after 2018.
- H2j: SIS/ICFs, including flowcharts or visual elements, are shorter in word count.

2.2. Data Collection, Data Sources, and Selection Criteria

To ensure regulatory consistency, this study included only trials clearly governed by a single legal framework. Transition trials (i.e., trials initially authorized under Directive 2001/20/EC and later transferred into CTIS) were explicitly excluded to avoid dual attribution. The final dataset, therefore, comprised only 1. legacy trials under the Directive registered in EudraCT, and 2. trials newly authorized under the Clinical Trials Regulation via CTIS. All trials were identified using their EU Clinical Trial Number (EUCT number) in the format YYYY-NNNNNN-CC-00. (20,22)

General inclusion criteria (applicable to both experiments):

- Trials registered in EudraCT or CTIS
- Availability of ICFs in German language
- Documents convertible into editable/ processable Word format without loss of structure

General exclusion criteria (applicable to both experiments):

- Documents with extensive redactions or technical issues (e.g., unreadable post-PDF conversion)
- ICFs that could not be reliably processed using Microsoft Word's word count tools
- Pediatric forms intended for direct reading by children
- Observational studies / non-interventional post-marketing studies
- Standalone medical device studies
- Non-interventional clinical studies or low-intervention studies
- Transition trials (Clinical trials initially authorized under Directive 2001/20/EC (and recorded in EudraCT) and formally transitioned into the Clinical Trials Information System (CTIS) to fall under Regulation (EU) No. 536/2014).

Where multiple versions of ICFs existed for the same study population (e.g., adult, adolescent, international versions, ...), the most comprehensive and representative version was selected for analysis.

2.2.1. Initial Data Collection Experiment 1:

Inclusion criteria Experiment 1:

In both subgroups, trials were identified via CTIS using structured queries:

- **Phase 1/2: 16 trials → 19 ICFs**
- **Phase 3: 16 trials → 24 ICFs**

Phase 1/2 Studies:

- CTIS-search criteria:
    - Overall trial status:
        - Authorised, recruiting
        - Authorised, recruitment pending
        - Ongoing, recruiting
        - Ongoing, recruitment ended
        - Ended
        - Temporarily halted
    - Locations: Austria, Germany
    - Status in the selected country:
        - Authorised, recruiting
        - Ongoing, recruiting
        - Ongoing, recruitment ended
        - Ended
        - Authorised, recruitment pending
        - Temporarily halted
    - Trial phase:
        - Human Pharmacology (Phase I) – First administration ...
        - Human Pharmacology (Phase I) – Other
        - Phase I and Phase II (Integrated) – Other
        - Phase I and Phase II (Integrated) - First administration ...
    - Transition trial: NO
    - *Rest: Blank*

402 results → 16 studies that met all criteria were evaluated (All available German and Austrian representative ICF for all 16 studies were evaluated → 19 ICF)

Phase 3 Studies:

- CTIS-search criteria:
    - Overall trial status:
        - Authorised, recruiting
        - Authorised, recruitment pending
        - Ongoing, recruiting
        - Ongoing, recruitment ended
        - Ended
        - Temporarily halted
    - Locations: Austria, Germany
    - Status in the selected country:
        - Authorised, recruiting
        - Ongoing, recruiting
        - Ongoing, recruitment ended
        - Ended
        - Authorised, recruitment pending
    - Trial phase:
        - Therapeutic confirmatory (Phase III)
    - Low intervention trial: NO
    - Date:
        - From: 01.01.2023
        - To: 27.03.2025
    - Transition trial: NO
    - Trial region: In both EEA and non-EEA
    - *Rest: Blank*

419 results → 16 studies that met all criteria were evaluated (All available German and Austrian representative main ICF for all 16 studies were evaluated → 24 ICF)

2.2.2. Initial Data Collection Experiment 2:

Inclusion criteria Experiment 2:

For Experiment 2, eligible studies were selected based on a structured manual search within the Ethics Committee Registry of the Medical University of Vienna (https://ekmeduniwien.at/core/catalog). The following inclusion criteria applied:

- Study phase: Phase III
- Therapeutic area: Oncology
- Submission route:
    - For the historical group (2011–2015): Submission via the ECS system (Ethics Committee System Austria)
    - For the recent group (2022–2025): Submission also via CTIS (Clinical Trials Information System), but also identifiable via the Ethics Committee Registry
- Study location: Austria (submitted and approved by the Ethics Committee of the Medical University of Vienna)
- Document availability: Study Information Sheets (SIS) and Informed Consent Forms (ICFs) retrievable via EK-number from institutional systems
- Language: German-language documents

A total of 12 studies per period (12 historical, 12 recent; separated by an approximately 10-year interval) were selected, resulting in 24 studies in total for comparison.

- **Pre-GDPR: 12 trials (2011–2014)**
- **Post-GDPR: 12 trials (2022–2024)**

2.3. Quantitative and descriptive parameters of both experiments

All variables were extracted and categorized based on predefined coding matrices that included structural, quantitative, and content-based variables across several dimensions such as risk and benefit communication, data protection, and biobanking. A detailed overview of all items, coding categories, ICF segments, and operational definitions can be supplied by the author.

Separate coding frameworks were developed for Experiment 1 and Experiment 2, tailored to the respective analytical focus. Structural attributes (e.g., study phase, sponsor type, therapeutic area) and metadata (e.g., page/word count, flowcharts, signature forms) were systematically extracted using web browsers, Microsoft Word, and PDF24. Special sections like risk-benefit communication, biobanking, and data protection were analyzed in separate Excel evaluation tables using standardized methodology, like the allocation of ICFs according to their attributes to defined linguistically described categories. Coding protocols were applied consistently, and ambiguous cases were resolved via team discussion and cross-validation.

Special Procedures for Complex Sections (Biobanking, Data Protection, and Risk Content):

Due to the structural heterogeneity of SIS/ICFs, particularly in the domains of biobanking, data protection, and risk communication, a more refined analytical framework was developed to enable systematic comparison across documents.

Biobanking:

The coding strategy for biobanking content was based on a four-level classification system, which distinguishes between:

- 1. explicitly labelled biobanking sections
- 2. mixed sections overlapping with data protection content
- 3. separate biobanking relevant consent elements or checkbox decisions
- 4. unlabeled or loosely embedded biobanking content

For each ICF, five different biobanking-related word counts were calculated to allow for cross-sectional comparison.

- 1. Biobanking only (incl. consent elements): All biobanking-specific body text wherever it appears in the document, including consent elements referring to biobanking and content extracted from within mixed/combined sections. Non-biobanking words inside mixed text are excluded.
- 2. Biobanking only (excl. consent elements): As in 1. but excluding consent elements
    - Used a lot for evaluation because it is the only “puristic word count” that consists only of pure biobanking information.
- 3. Dedicated biobanking section: All words within a clearly labelled biobanking section, even if individual sentences co-present other topics.
    - This word count was not often used for evaluation because biobanking content was frequently in mixed sections, which distorted outcomes
- 4. Biobanking consent elements: Words in biobanking-specific consent elements/checkbox decisions and any directly adjacent consent text, wherever located.

- 5. Total biobanking content: All biobanking content, including consent forms and biobanking content inside and outside of the main biobanking section, also including all content of combined sections
    - For the same reason as in 3, this was rarely used for evaluation

Counts are based on body text only (headers and footers excluded). In overlapping passages (e.g., mixed data-protection/biobanking text), biobanking-specific sentences or clauses were isolated and assigned to the relevant metric. Primary analyses mainly use 2, 4, and 5. The five metrics are "neither mutually exclusive nor algebraically additive"; each was computed directly, rather than derived from other counts.

Data Protection:

A similar layered strategy was applied to data protection content, where four separate word count categories were established:

- 1. Main data protection section without consent forms
- 2. Data protection section + scattered data protection text
- 3. Consent forms with data protection content
- 4. Total cumulative data protection content

Risk Content (including pregnancy-related risks):

Risk sections also showed high structural variability, particularly with regard to the inclusion and placement of pregnancy and contraception-related information. Pregnancy risks were commonly addressed when female participants of reproductive potential (WOCBP) were eligible for the study. Content typically included potential teratogenic effects of the investigational product, contraception requirements and side effects, consequences of becoming pregnant during the trial, and early termination of participation due to pregnancy. However, these elements were inconsistently placed across documents.

Pregnancy and contraception-related risks were variously located within the main risk section, in separate dedicated blocks (e.g., "Information for Women of Childbearing Age"), or embedded in general sections such as "Who Is Not Allowed to Participate" or "What Happens If I or My Partner Gets Pregnant". In some cases, multiple such elements were distributed across different sections. This lack of consistent structure posed challenges for comparative word count analysis and required manual assignment of pregnancy-related content to either the main risk section or to thematically designated subsections based on semantic relevance. As with biobanking and data protection, a layered coding approach was applied to capture this heterogeneity.

- 1. Word Count risk (without extensive pregnancy and/or contraception risk): (Mainly used for analysis)
- 2. Pregnancy and/or contraception risk word count
- 3. Word count risk (total): 1+2

To ensure consistency and reproducibility, all coding decisions follow predefined semantic and structural criteria. Minor interpretation was applied in “hybrid cases”, and word counts always excluded headers and footers text.

All coding procedures were performed by a single coder (the author). To maintain reliability, coding rules were strictly derived from predefined matrices, and ambiguous classifications were resolved via iterative self-validation and cross-referencing within the dataset.

2.4. Statistical Analysis

Quantitative data was analyzed using descriptive statistics, independent samples **t-tests** (for group comparisons), and **regression models** where applicable. When dependent variables were ordinal and group comparisons did not justify the use of means, non-parametric alternatives such as the **Mann–Whitney U test** were applied. Numerical datasets were generally reported as mean ± standard deviation, whereas categorical or dichotomous variables were presented as frequencies and percentages. For paired binary variables (e.g., presence vs. absence of a risk summary section in AT vs. DE ICFs), McNemar’s test was applied.

All text coding and quantitative text extractions were conducted using Microsoft Word and manual review protocols, with additional cross-validation steps for ambiguous cases. All statistical analyses (incl. all graphs and visualizations) were performed by the author in a test version of GraphPad Prism 10.5.0 (GraphPad Software, San Diego, CA, USA) for Windows, with supplementary processing in Microsoft Excel. Tests not directly supported by GraphPad Prism (e.g., the McNemar test) were also conducted by the author using appropriate alternative methods. A detailed overview of the variable definitions and coding categories, as well as the GraphPad Prism files, can be supplied by the author.

2.4.1. Graphical Representations and Data Visualization:

All figures presented in this thesis were generated using GraphPad Prism (Version 10.5.0, GraphPad Software, San Diego, CA, USA) for Windows. This software was used for the creation of statistical plots and visualizations to summarize and illustrate the results of the quantitative and qualitative analyses. Across all figure types, axis labels, legends, and annotations were designed to ensure interpretability, also without requiring reference to the main text. All graphical representations were created from processed datasets derived from the coding matrices described in the “Data Collection” section. The figure types and their respective purposes are described below to provide methodological transparency and facilitate interpretation.

Pie Charts

Pie charts are used to depict the proportion of categories within a whole, expressed as percentages. Each slice represents a distinct category (e.g., the proportion of informed consent forms containing a specific content element), and the size of the slice is proportional to its relative frequency. This format allows for a quick visual assessment of distribution patterns within categorical variables. Colors in the legend (displayed on the right) are listed in the exact order of the slices, starting at the 12 o’clock position and proceeding clockwise.

Bar Charts

Bar charts display the absolute or relative frequency of discrete categories. In this thesis, bar charts were also used to compare the presence, absence, or frequency of specific document characteristics (e.g., inclusion of visual elements, dedicated sections) between groups. Bar lengths are proportional to the measured value.

Estimation Plots

Estimation plots were generated in GraphPad Prism to visualize group comparisons in combination with effect size estimation. The left panel of each plot shows the raw data distribution for the two groups being compared (e.g., Phase 1/2 vs. Phase 3), with each dot representing one data point. A horizontal dashed line indicates the mean of the respective group. The right panel displays the mean difference between groups, accompanied by a vertical error bar representing the 95 % confidence interval (CI) of this difference. Positive values indicate higher means in the second group, while negative values indicate higher means in the first group. Statistical inference was based on two-tailed unpaired t-tests, often with the exact p-value, mean difference ± standard error of the mean (SEM), and 95 % CI reported in the figure legends. This format allows the reader to simultaneously assess the raw data distribution, the magnitude of the difference, and the uncertainty around that estimate, in line with current recommendations to report effect sizes alongside p-values.

Scatter Plots and Simple Linear Regression

Scatter plots were used to visualize the relationship between two continuous variables, with each point representing one observation. Where applicable, a simple linear regression line was fitted to the data to summarize the trend. Statistical parameters of the regression (slope, intercept, coefficient of determination R^2, and p-value) were computed by GraphPad Prism and often reported in the corresponding figure legends or results text.

Heatmaps

Heatmaps are used to visualize the presence/absence or magnitude of specific characteristics across multiple items. Color coding gradient scales (red/green) provide an immediate visual cue for the occurrence or intensity of each variable, with the exact coding scheme defined in the figure legend.

2.5. Artificial Intelligence (AI) and Additional Tools and Resources

In this thesis, ChatGPT by OpenAI was employed exclusively as a supportive tool for translation, grammar refinement, minor content enhancement, as well as for searching datasets and quickly identifying and/or cross-referencing specific details. The interaction with ChatGPT involved formulating targeted prompts, reviewing its responses, and critically assessing the proposed revisions. All suggestions were evaluated for accuracy and appropriateness and, where suitable, rephrased or adapted to fit the context. The outputs served solely to support, complement, and accelerate the author's own work, with the aim of improving the overall quality of the thesis.

For additional proofreading and error correction, Grammarly (Grammarly Inc., San Francisco, CA, USA) was used.

The literature references were managed and formatted using the reference management software Zotero.

Ethical Considerations:

All documents analyzed were publicly accessible or obtained via official registries and converted for textual analysis. This study did not involve any patient data. Therefore, this project did not require additional ethical approval under Austrian or German research legislation for secondary document analysis.

3. Results

3.1. Baseline Characteristics

3.1.1. Experiment 1 by Study Phase:

Table 1: Study- and ICF-Level Characteristics (Experiment 1): Frequency Data

Baseline Characteristics	**Phase 1/2 (N=19)**	**Phase 3 (N=24)**
Study specific characteristics		
Studies with one trial site in AT	5 (26.3%)	8 (33.3%)
Studies with one trial site in DE	14 (73.7%)	16 (66.7%)
Academic sponsors	3 (15.8%)	0 (0%)
Industry sponsors	16 (84.2%)	24 (100%)
Other sponsor types	0 (0%)	0 (0%)
Use of placebo and/or sham intervention	3 (15.8%)	14 (58.3%)
Inclusion of standard treatment arm	0 (0%)	12 (50%)
No established standard of care	4 (21.1%)	2 (8.33%)
Therapeutic areas		
Diseases [C] - Neoplasms [C04]	12 (63.2%)	11 (45.8%)
Diseases [C] - Hemic and Lymphatic Diseases [C15]	3 (15.8%)	2 (8.3%)
Analytical, Diagnostic and Therapeutic Techniques and Equipment [E] - Therapeutics [E02]	2 (10.5%)	0 (0%)
Musculoskeletal Diseases [C05]	1 (5.3%)	1 (4.2%)
Diseases [C] - Skin and Connective Tissue Diseases [C17]	1 (5.3%)	0 (0%)
Diseases [C] - Digestive System Diseases [C06]	6 (31.6%)	5 (20.8%)
Diseases [C] - Nervous System Diseases [C10]	2 (10.5%)	4 (16.7%)
Diseases [C] - Respiratory Tract Diseases [C08]	3 (15.8%)	5 (20.8%)
Diseases [C] - Male Urogenital Diseases [C12]	1 (5.3%)	0 (0%)
Diseases [C] - Immune System Diseases [C20]	1 (5.3%)	4 (16.7%)
Diseases [C] - Urogenital Diseases [C12]	1 (5.3%)	0 (0%)
Diseases [C] - Eye Diseases [C11]	0 (0%)	3 (12.5%)
Diseases [C] - Otorhinolaryngologic Diseases [C09]	1 (5.3%)	1 (4.2%)
Phenomena and Processes [G] - Genetic Phenomena [G05]	0 (0%)	1 (4.2%)
Diseases [C] - Congenital, Hereditary, and Neonatal Diseases and Abnormalities [C16]	0 (0%)	2 (8.3%)
SIS/ICF specific characteristics		
Flow charts	2 (10.5%)	9 (37.5%)
Cartoons	3 (15.8%)	4 (16.7%)
tables	17 (89.5%)	22 (91.7%)
table of contents	9 (47.4%)	11 (45.8%)

- Disease categories are harmonized beyond registered CTIS classification, as entries in CTIS may inconsistently reflect organ-specific disease classes alongside Neoplasms [C04]
- For some studies, both Austrian (AT) and German (DE) ICF versions were analyzed. As a result, certain study-level characteristics are represented twice in this table, which may lead to an overrepresentation of bi-national or multinational studies. Alternative presentations of the baseline characteristics can be provided by the author upon request.

Table 2: Study- and ICF-Level Characteristics (Experiment 1): Numeric Data (Mean ± SD) by study phase

Baseline Characteristics of SIS/ICFs	Phase 1/2 (N=19)	Phase 3 (N=24)
Study specific characteristics		
Overall number of countries involved	3.58 (+-2.14)	10.57 (+-3.19)
SIS/ICF specific characteristics		
redaction (1=low/2=medium/3=high)	1.21 (+-0.42)	1.17 (+-0.38)
Number of SIS/ICFs per study	3.05 (+-1.35)	3.75 (+- 1.85)
number of main ICFs	1.16 (+-0.37)	1.04 (+-0.20)

3.1.2. Experiment 2 by year of ICF:

Table 3: Study- and ICF-Level Characteristics (Experiment 2): Frequency Data

Baseline Characteristics	2011-2014 (N=12)	2022-2024 (N=12)
Study specific characteristics		
Studies with one trial site in AT	12 (100%)	12 (100%)
Academic sponsors	3 (25%)	1 (8.3%)
Industry sponsors	9 (75%)	12 (100%)
Other sponsor types	0 (0%)	0 (0%)
Study phase 3	12 (100%)	12 (100%)
Use of placebo and/or sham intervention	6 (50%)	3 (25%)
Inclusion of standard treatment arm	7 (58.3%)	10 (83.3%)
No established standard of care	3 (25%)	0 (0%)
Therapeutic areas		
Neoplasm/oncology	12 (100%)	12 (100%)
SIS/ICF specific characteristics		
Flow charts	2 (16.7%)	3 (25%)
Cartoons	0 (0%)	2 (16.7%)
tables	2 (16.7%)	12 (100%)
table of contents	0 (0%)	1 (8.3%)

Table 4: Study- and ICF-Level Characteristics (Experiment 2): Numeric Data (Mean ± SD)

Baseline Characteristics	2011-2014 (N=12)	2022-2024 (N=12)
Study specific characteristics		
study population number	729.6 (+-762.9)	543.8 (+-297.7)
SIS/ICF specific characteristics		
redaction (1=low/2=medium/3=high)	1 (+-0)	1 (+-0)

3.2. Experiment 1

3.2.1. Main Hypothesis:

H1: There is a significant difference in total word count and page count between SIS/ICFs for Phase 1/2 and Phase 3 clinical trials.

- Unpaired two-tailed t-tests were conducted. The analysis revealed no statistically significant difference between the two groups in terms of total word count ($t(41) = 0.78$, $p = 0.441$) or page count ($t(41) = 0.64$, $p = 0.524$). The mean page count was 31.47 pages for Phase 1/2 ICFs and 33.17 pages for Phase 3 ICFs. The mean word count was 10739 words for Phase 1/2 ICFs and 11445 words for Phase 3 ICFs.
- *A possible confounding effect must be considered when interpreting these results. Phase 3 trials are substantially more multicentric and typically involve a higher number of countries (see H1g), which could independently increase ICF length through the inclusion of additional regulatory references, country-specific requirements, and more standardized multinational templates. This internationalization may therefore partly account for the descriptive tendency toward longer ICFs in Phase 3 trials. In addition, trial design features such as the frequent implementation of placebo or standard treatment arms in later phases may further contribute to word and page count.*

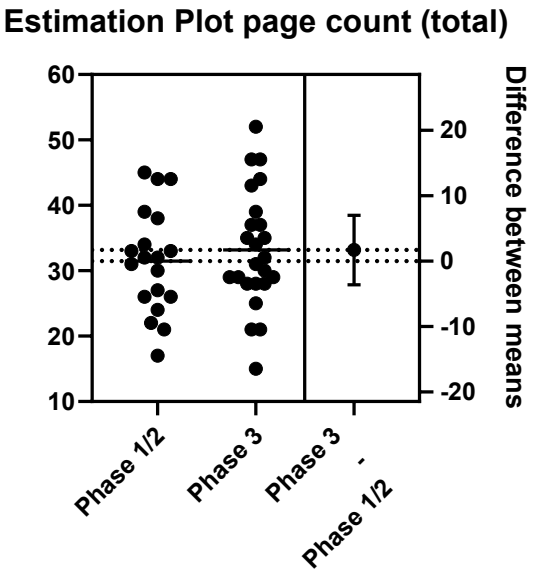

Figure 3.1: Comparison of the total page count of ICFs between Phase 1/2 and Phase 3 clinical trials. No statistically significant difference was found ($t(41) = 0.64$, $p = 0.524$).

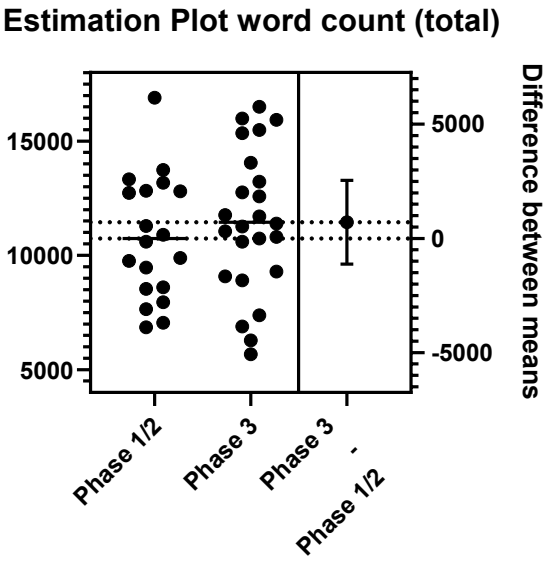

Figure 3.2: Comparison of the total word count of ICFs between Phase 1/2 and Phase 3 clinical trials. No statistically significant difference was found ($t(41) = 0.78$, $p = 0.441$).

3.2.2. Secondary Hypotheses:

H1a: SIS/ICFs for Phase 3 trials are longer (in word and page count) than those for Phase 1 trials.

- As shown in the statistical analysis for the main hypothesis (H1), ICFs for Phase 3 trials show a slight but statistically non-significant increase in word and page count compared to Phase 1 ICFs.

H1b: Risk communication sections (in word count and page count) are more extensive in Phase 1 SIS/ICFs than in Phase 3 SIS/ICFs.

- Analysis of risk-section length. We used unpaired, two-tailed t-tests to compare the length of the risk sections (pages and words) between Phase 1/2 and Phase 3 ICFs. To ensure comparability, extensive pregnancy/contraception subsections inside of the risk section were excluded from the counts; brief mentions within the risk section were retained. No statistically significant differences were observed in word count (t(41)=0.4319, p=0.6681) or page count (t(41)=0.9890, p=0.3285). Mean page counts were 4.6 pages (Phase 1/2) vs 5.5 pages (Phase 3); mean word counts were 1,698 (Phase 1/2) vs 1,833 (Phase 3).

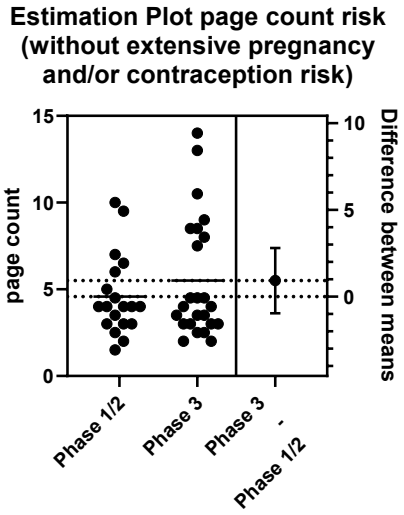

Figure 3.3: Comparison of the page count of the risk section between Phase 1/2 and Phase 3 clinical trials. No statistically significant difference was found (t(41) = 0.9890, p = 0.3285).

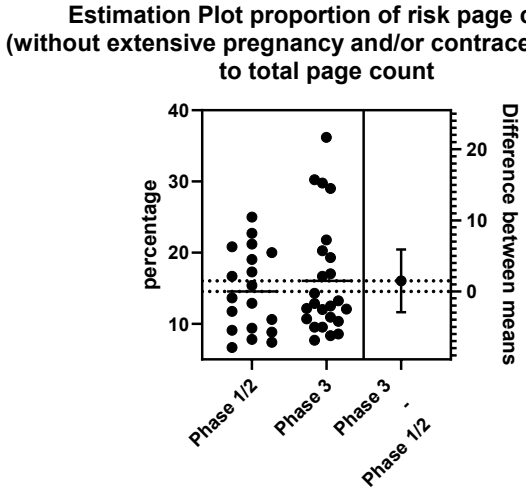

Figure 3.4: Proportion of the risk section page count relative to total ICF length in Phase 1/2 and Phase 3 trials (t(41) = 0.6907, p = 0.4937). The mean proportions were 14.54% (Phase 1/2) and 16.05% (Phase 3)

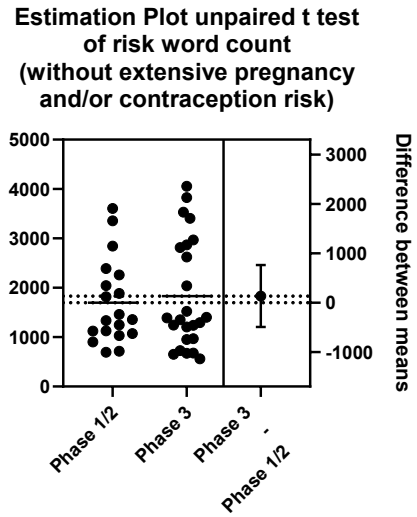

Figure 3.5: Word count of the risk section (excluding extensive pregnancy-related risks) in Phase 1/2 and Phase 3 informed consent forms. No statistically significant difference was found (t(41) = 0.4319, p = 0.6681). The average word count was 1,698 for Phase 1/2 and 1,833 for Phase 3, with a non-significant mean difference of 134 words (± 311.2). The effect size was minimal (η^2 = 0.0045).

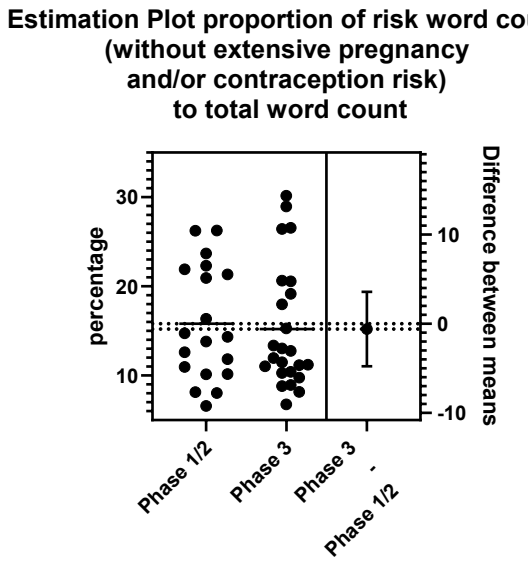

Figure 3.6: Proportion of risk-related word count (excluding pregnancy risks) relative to total ICF word count in Phase 1/2 and Phase 3 trials. (t(41) = 0.2920, p = 0.7718). The average proportion was 15.81% for Phase 1/2 and 15.21% for Phase 3.

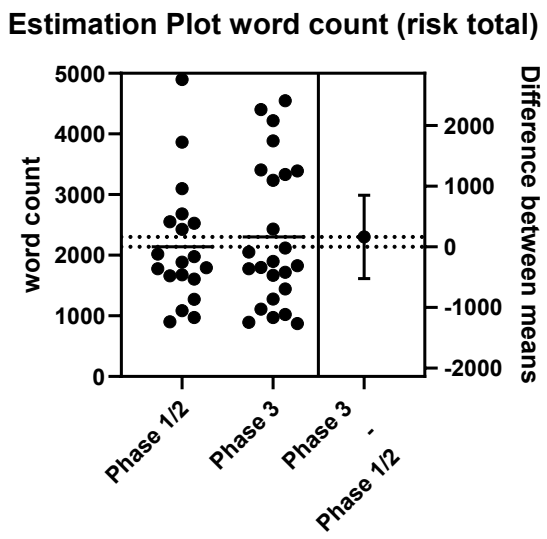

Figure 3.7: Total word count of the risk section (including pregnancy-related content) in Phase 1/2 and Phase 3 informed consent forms (t(41) = 0.4788, p = 0.6346). Phase 1/2 ICFs had a mean of 2,141 words, compared to 2,304 words in Phase 3. The mean difference of 163 words (± 340.5) was not statistically significant, and the effect size was small (η^2 = 0.0056).

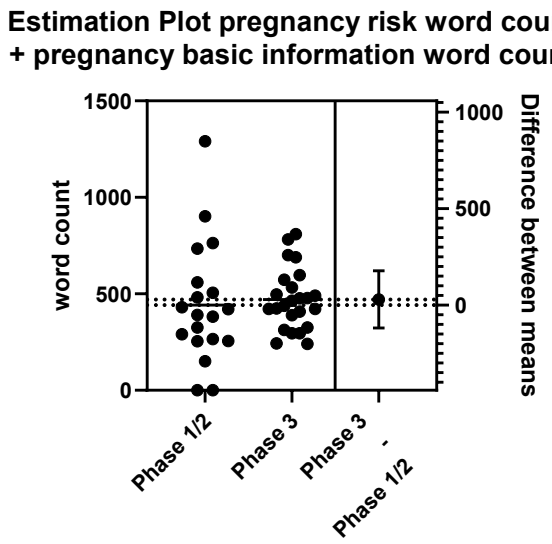

Figure 3.8: Comparison of the combined word count for pregnancy-related risk and basic pregnancy information between Phase 1/2 and Phase 3 informed consent forms (t(41) = 0.3907, p = 0.6980).

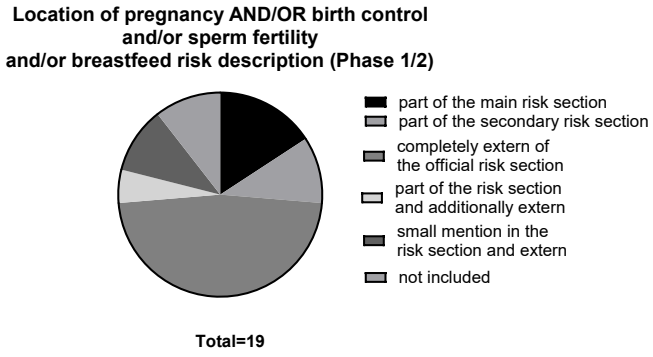

Figure 3.9: Placement of pregnancy-, contraception-, fertility-, and breastfeeding-related risk information in Phase 1/2. The chart categorizes where in the document such information was found (e.g., within the risk section, separate safety sections, or embedded in other areas).

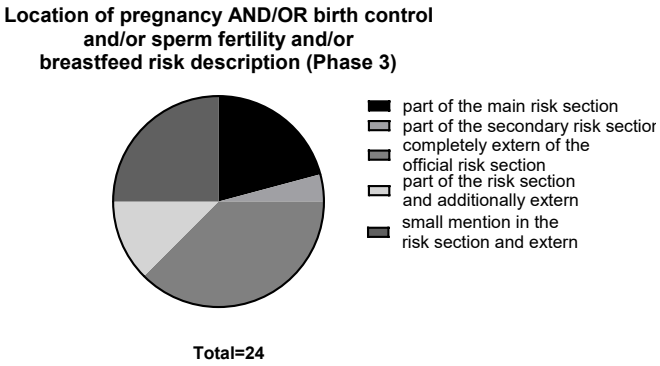

Figure 3.10: Placement of pregnancy-, contraception-, fertility-, and breastfeeding-related risk information in Phase 3.

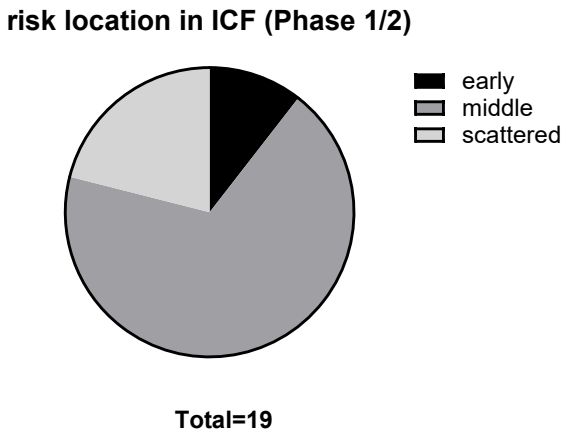

Figure 3.11: Distribution of risk information within informed consent forms (ICFs) for Phase 1/2 trials (n=19). Most often, risks were described in the middle of the document, while a minority appeared either early or scattered throughout the ICF.

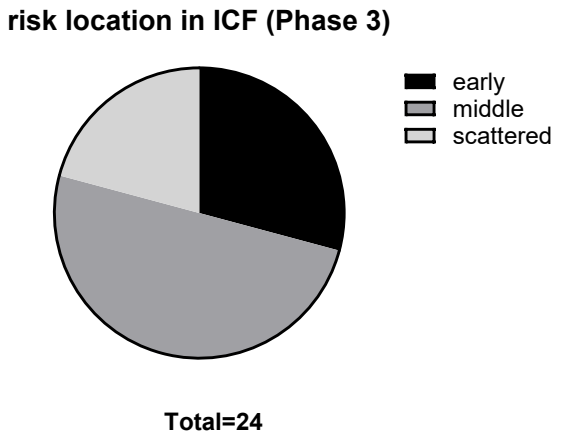

Figure 3.12: Distribution of the risk information location within informed consent forms (ICFs) for Phase 3 trials (n=24). Compared to Phase 1/2, risks were more frequently placed early in the document, though the majority still appeared in the middle.

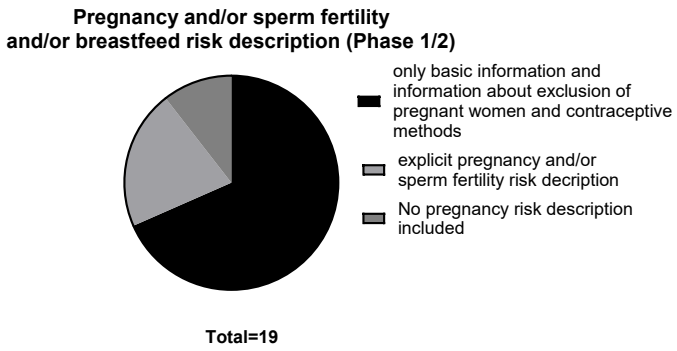

Figure 3.13: Degree of content-related detail in the description of pregnancy-, fertility-, or breastfeeding-related risks in SIS/ICFs from Phase 1/2 clinical trials. (1 of 2 ICFs without pregnancy risk description did not include female participants/ see Figure 10.3)

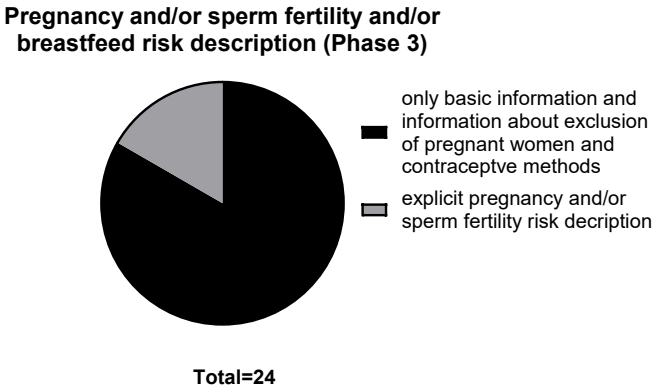

Figure 3.14: Degree of detail in the description of pregnancy-, fertility-, or breastfeeding-related risks in SIS/ICFs from Phase 3 clinical trials.

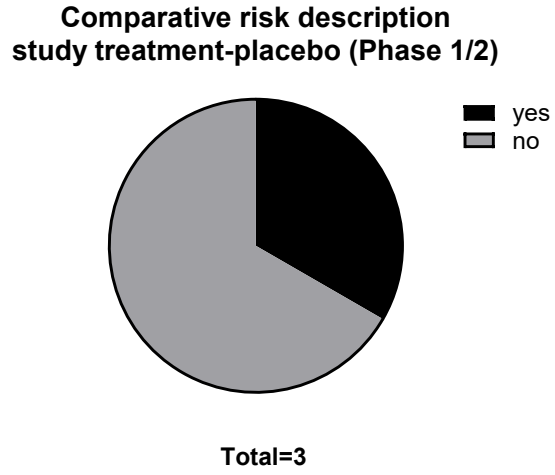

Figure 3.15: Proportion of ICFs from Phase 1/2 trials that included a placebo or sham procedure in the study design (n = 3), which also provided a comparative risk description between the investigational treatment and the placebo. One of three included such a comparative description.

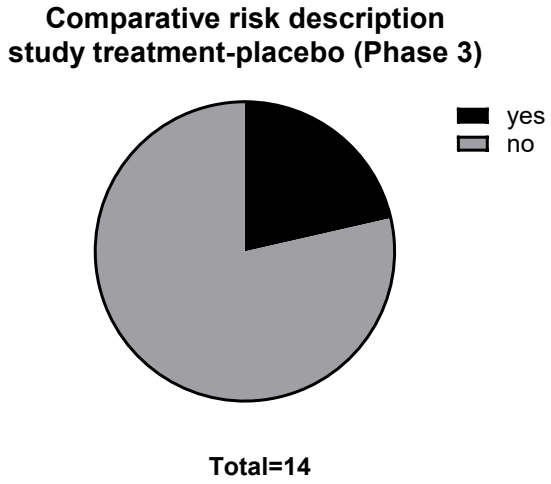

Figure 3.16: Proportion of ICFs from Phase 3 trials with placebo or sham procedures (n = 14) that contained a comparative risk description. The majority (79%) did not include a comparison of potential risks between investigational treatment and placebo.

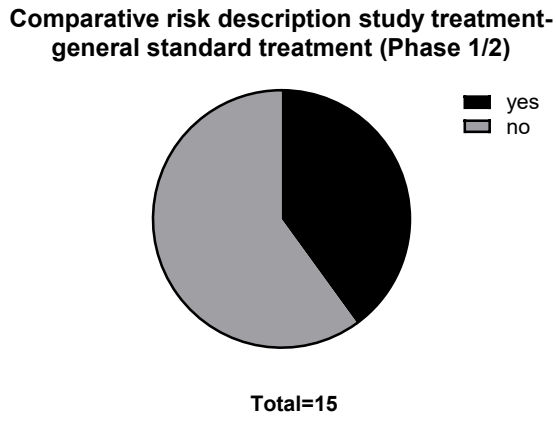

Figure 3.17: Pie chart showing the proportion of informed consent forms (ICFs) from Phase 1/2 studies that included a comparative risk description between the investigational treatment and the standard treatment, in cases where a standard treatment was available and not explicitly excluded. 6 of 15 ICFs provided such a comparison.

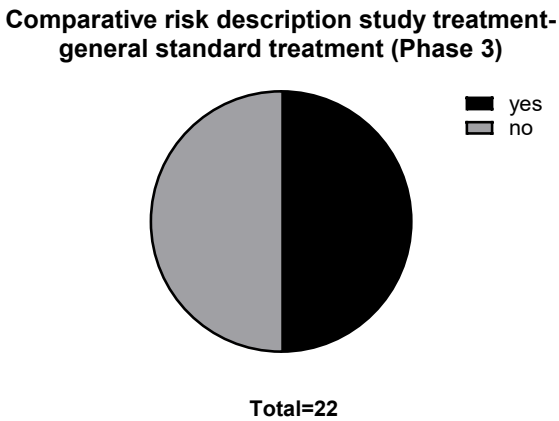

Figure 3.18: Pie chart illustrating the share of Phase 3 ICFs that contained a comparative risk description between the investigational treatment and standard treatment, in cases where a standard treatment was available and not explicitly excluded. An equal split was observed, with 11 of 22 ICFs (50%) including such information.

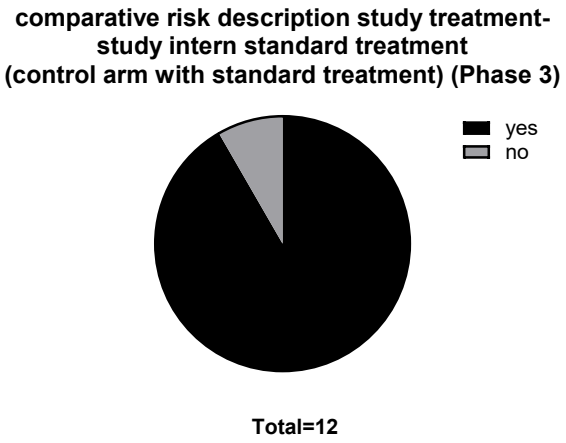

Figure 3.19: Comparative risk description between study treatment and study-internal standard treatment in Phase 3 trials. Only Phase 3 trials with an internal standard treatment arm were included in this analysis (n=12). Such studies were not observed in the Phase 1/2 group, which is why no comparison could be made for that subgroup. A clear majority (91.7%) of these ICFs provided a comparative risk description between the investigational treatment and the study's own standard treatment arm, while only 1 out of 12 did not.

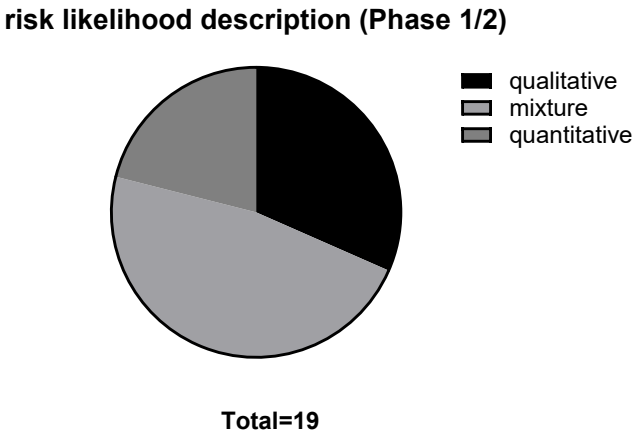

Figure 3.20: Distribution of risk likelihood descriptions in Phase 1/2 ICFs. Risks were most commonly described using a combination of qualitative and quantitative elements ("mixture"), followed by purely qualitative and purely quantitative descriptions (n = 19).

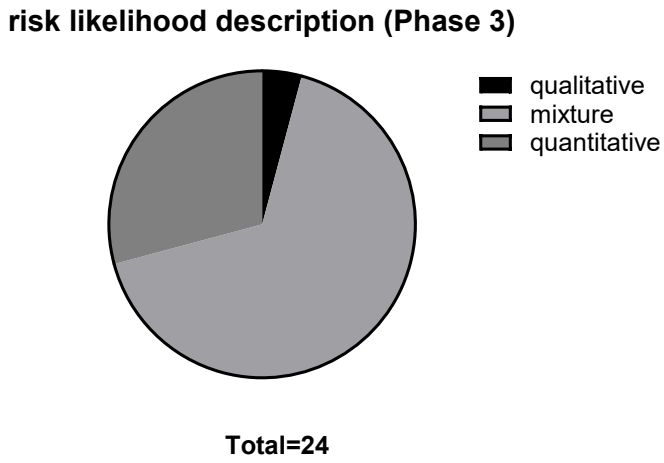

Figure 3.21: Distribution of risk likelihood descriptions in Phase 3 ICFs.

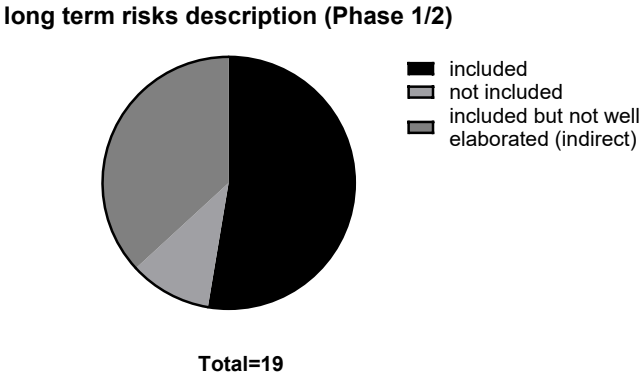

Figure 3.22: This chart illustrates how long-term risks were described in the consent forms of Phase 1/2 studies. In contrast to immediate/acute risks, which were addressed in all ICFs, long-term risks were often omitted or only indirectly mentioned.

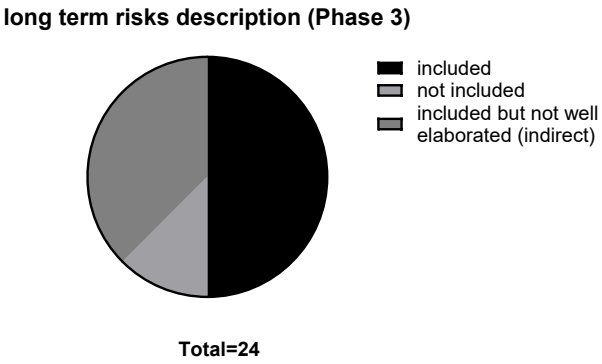

Figure 3.23: This chart shows the inclusion and quality of long-term risk descriptions in Phase 3 ICFs. As with Phase 1/2, immediate/acute risks were consistently included in all consent documents, whereas long-term risks were less consistently and often less explicitly addressed

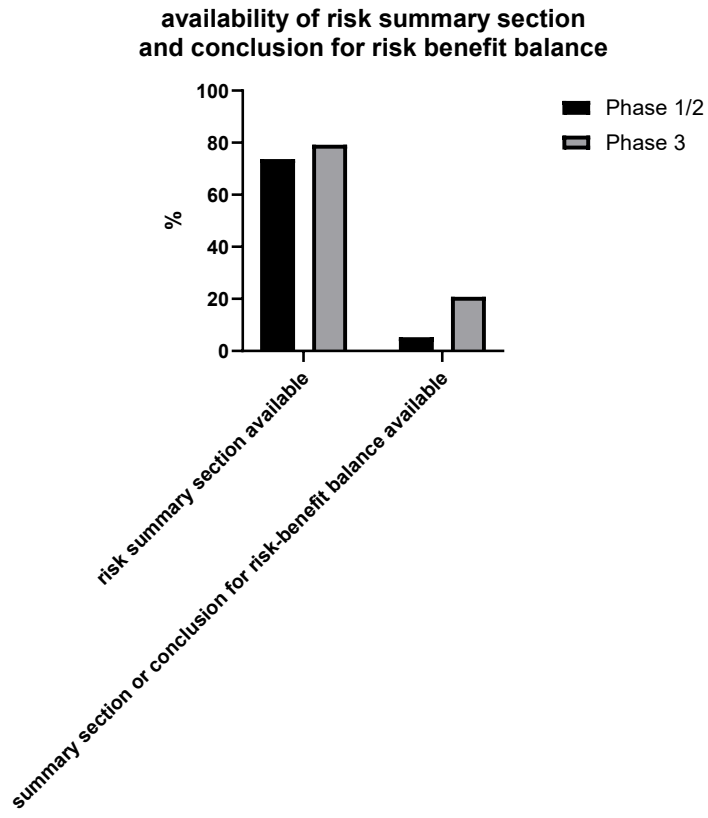

Figure 3.24: Availability of dedicated sections addressing risk and risk-benefit balance in ICFs across trial phases. The majority of ICFs from both Phase 1/2 and Phase 3 studies included a risk summary section (≥70%), while only a small proportion provided a concluding section explicitly discussing the overall risk-benefit balance. Such conclusions were more frequent in Phase 3 trials (20.8%) than in Phase 1/2 (5.3%). One ICF in each group contained a relatively elaborate reflection on the overall risk-benefit balance. In one case, however, the risk-benefit balance section replaced both a separate risk section and a benefit section, rather than serving as an additional extension. In some instances, the risk-benefit balance was realized through a single, unified summary of the entire ICF, without subdivisions or dedicated headings.

H1c: The ICF-reported likelihood of severe adverse effects is higher in Phase 1/2 than in Phase 3 trials.

- A Mann–Whitney U test was conducted on the ordinal probability ratings. The results showed no statistically significant difference between the two groups (U = 223, p = 0.916). The median rating for both Phase 1/2 and Phase 3 trials was identical (Median = 3.00 for both groups; Phase 1/2: n = 19; Phase 3: n = 24). The Hodges–Lehmann estimate of the difference in medians was 0.00, indicating no shift in perceived risk level between the groups. These results do not support hypothesis H1c, suggesting that, based on the assessed ICFs, the probability of severe side effects is perceived similarly across Phase 1/2 and Phase 3 trials.

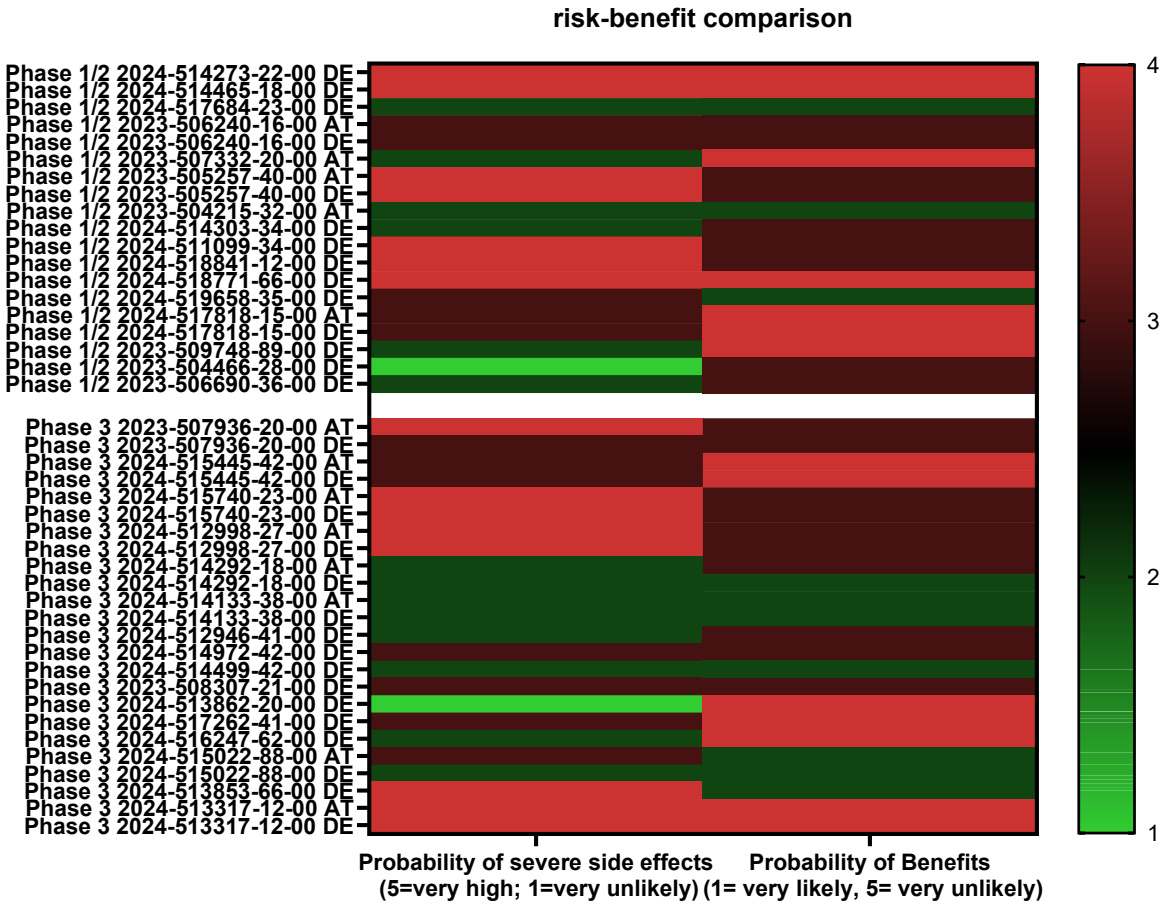

Figure 3.25: Heatmap of ICF-stated probability of severe side effects and probability of benefits across informed consent forms (ICFs) from Phase 1/2 and Phase 3 clinical trials. Each ICF was rated on a 5-point ordinal scale for both categories. Ratings were based on the language and presentation of risk and benefit in the patient information. Regarding the probability of severe side effects, no significant difference was found between the two groups (Mann–Whitney U = 223, p = 0.916)

H1d: The ICF-reported likelihood of benefits is higher in Phase 3 than in Phase 1/2 trials.

- A Mann–Whitney U test was conducted based on ordinal ratings extracted from the informed consent forms (ICFs). Each ICF was evaluated on a 5-point scale, reflecting the communicated likelihood of therapeutic benefit (see Figure 3.25). The analysis revealed no statistically significant difference between the two trial phases (U = 194, exact p = 0.4031). The median rating was identical in both groups (Median = 3.00; Phase 1/2: n = 19; Phase 3: n = 24). The Hodges–Lehmann estimate of the difference between medians was 0.00, indicating no notable shift in how potential benefits were presented across phases. While not statistically significant, the data suggests a slight tendency toward higher perceived benefit probability in Phase 3 trials.

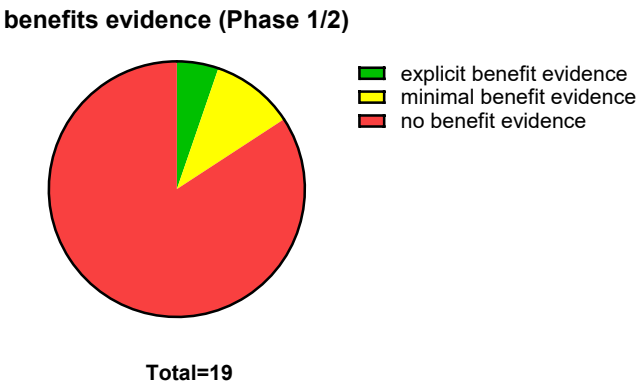

Figure 3.26: Evidence of described study benefits in ICFs of Phase 1/2 clinical trials (n = 19). Pie chart showing the degree to which the informed consent forms (ICFs) provided benefit-related evidence. The majority of ICFs provided no evidence (red), while minimal benefit evidence (yellow) and explicit benefit evidence (green) were rarely included.

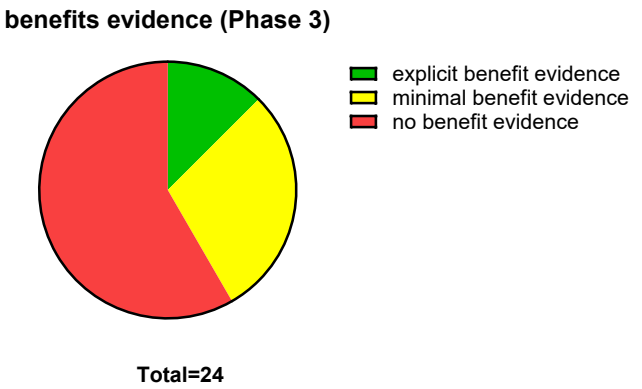

Figure 3.27: Evidence of described study benefits in ICFs of Phase 3 clinical trials (n = 24). Pie chart displaying the frequency of benefit evidence in Phase 3 ICFs. Compared to Phase 1/2, a higher proportion of documents included minimal or explicit benefit-related statements, although many still lacked any substantiated benefit claims.

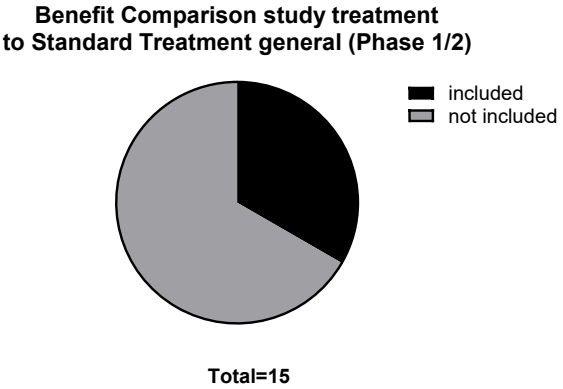

Figure 3.28: Proportion of Phase 1/2 SIS/ICFs in which the study treatment was compared to a general standard treatment with regard to benefit. ICFs were only included if a standard treatment was available and not explicitly ruled out.

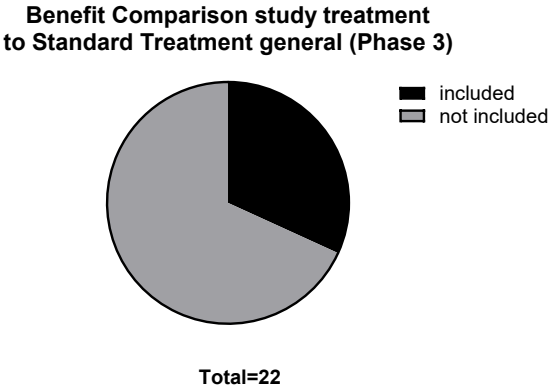

Figure 3.29: Proportion of Phase 3 informed consent forms (ICFs) in which the study treatment was compared to a general standard treatment with regard to benefit. ICFs were only included if a standard treatment was available and not explicitly ruled out.

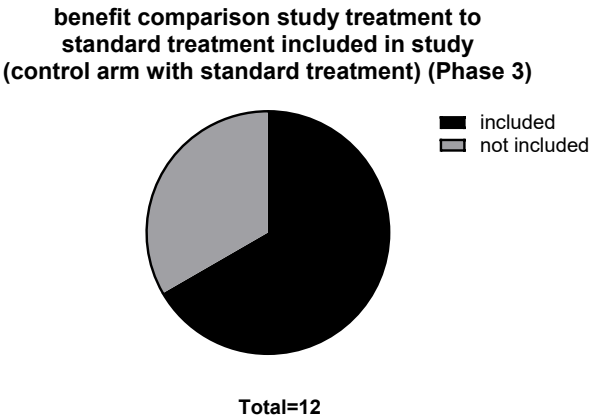

Figure 3.30: Proportion of Phase 3 informed consent forms (ICFs) in which a benefit comparison between the study treatment and a control arm standard treatment was explicitly included, in trials that featured a control arm with standard therapy (n = 12). All of the Studies in the Phase 1/2 group did not include a standard-arm. The informed consent form (ICF) for the 2024-517818-15-00 DE Phase Ib/II trial is unique within its study group. Although the study has no control arm and no standard or placebo therapy, the ICF nonetheless includes a benefit comparison between the investigational treatment and standard treatment/placebo. This is inconsistent with the actual study design and distinguishes it from other Phase 1/2 trials in the same dataset, none of which make such comparisons when a control arm is absent.

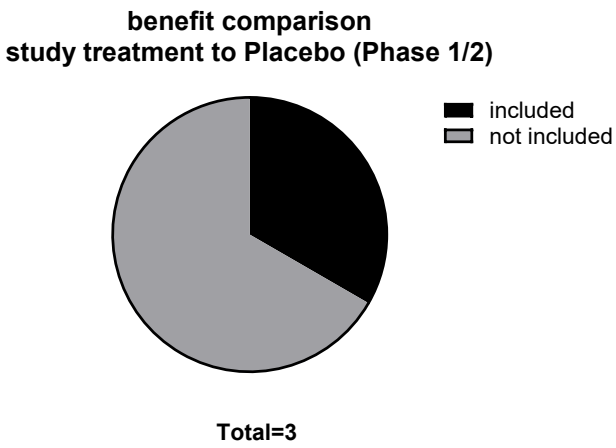

Figure 3.31: Proportion of Phase 1/2 informed consent forms (ICFs) from trials including a placebo arm (n = 3) that contained an explicit benefit comparison between the study treatment and placebo. In addition to these three placebo-controlled studies, the 2024-517818-15-00 DE Phase Ib/II trial (which lacks both a placebo and a standard treatment arm) was also part of the Phase 1/2 group. Remarkably, this trial's ICF included a benefit comparison to both standard treatment and placebo, even though such a comparison is not methodologically supported by the study design. The study was not taken into account for this Pie chart.

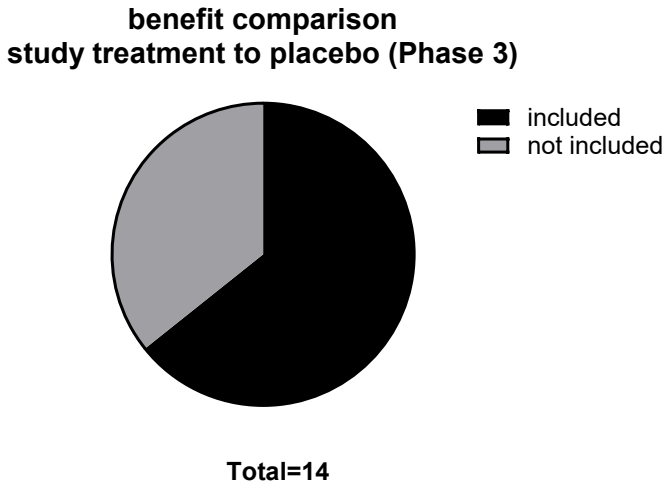

Figure 3.32: Proportion of Phase 3 informed consent forms (ICFs) from trials including a placebo arm (n = 14) that explicitly contained a benefit comparison between the study treatment and placebo.

- All the ICFs of Experiment 1 included "explanation of indirect benefits" and "statement on uncertainty of benefits"

H1e: The overall number of countries involved in a clinical trial is positively associated with the word count and/or page count of the informed consent form.

- Six separate linear regression analyses were conducted to examine whether the number of countries involved in a clinical trial was positively associated with the length of the informed consent form (ICF), measured both as total word count and as word count within the risk communication section (Only the risk word counts without extensive pregnancy and/or contraception risk description were used for the analysis). For Phase 1/2 trials, a significant positive association was observed between the number of countries and the total word count of the ICFs ($R^2 = 0.2590$, $p = 0.0261$), with an average increase of 641.4 words per additional country (regression equation: $Y = 641.4 \times X + 8444$). In contrast, for Phase 3 trials, the association was not significant ($R^2 = 0.0699$, $p = 0.2120$), and the estimated increase was lower (slope = 260.6 words). When combining both phases, the regression approached significance ($R^2 = 0.0903$, $p = 0.0503$), suggesting a borderline trend toward a global relationship (slope = 196.6 words per country).
- A similar pattern emerged when analyzing only the risk communication sections. For Phase 1/2, the number of countries was again significantly associated with increased risk-related word count ($R^2 = 0.3371$, $p = 0.0091$), with an estimated increase of 232.8 words per country ($Y = 232.8 \times X + 865{,}3$). In contrast, no significant association was found for Phase 3 ($R^2 = 0.055$, $p = 0.270$), and the combined regression across both phases remained non-significant ($R^2 = 0.0658$, $p = 0.0969$).
- These results partially support Hypothesis H1e: while the number of participating countries correlates with ICF length and risk communication content in Phase 1/2 trials, this effect appears to diminish in Phase 3.

Both phases combined	Phase 1/2	Phase 3
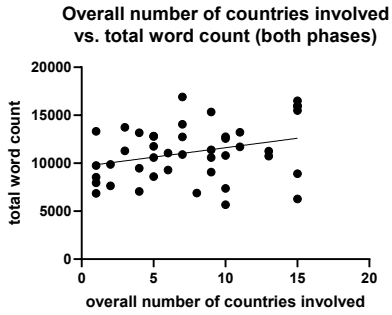	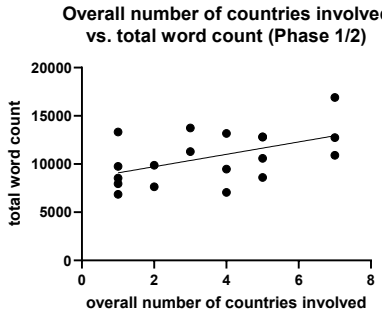	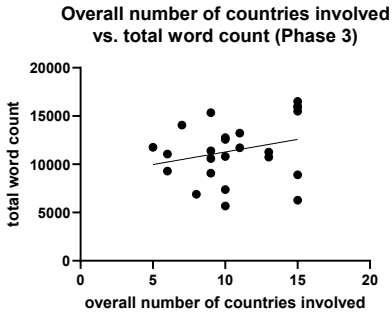
Figure 3.33: Scatterplot showing the relationship between the number of countries involved and the total word count of informed consent forms (ICFs) across all clinical trials (Phase 1/2 and Phase 3 combined).	*Figure 3.34: Scatterplot showing the relationship between the number of countries involved and the total word count of ICFs in Phase 1/2 clinical trials*	*Figure 3.35: Scatterplot showing the relationship between the number of countries involved and the total word count of ICFs in Phase 3 clinical trials.*
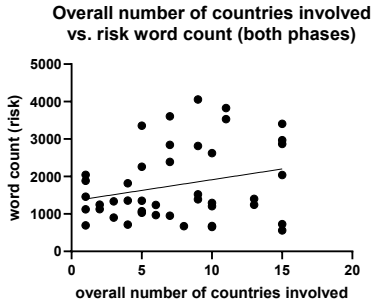	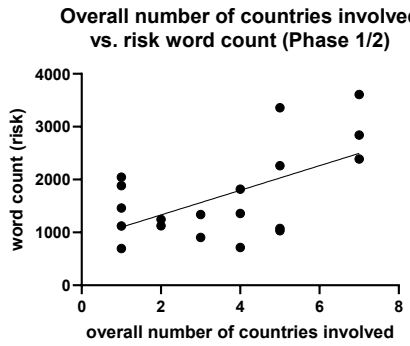	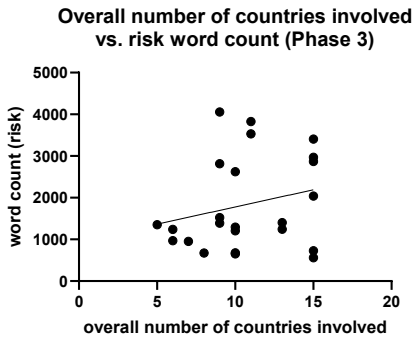
Figure 3.36: Scatterplot showing the relationship between the number of countries involved and the word count of the risk communication section in ICFs across all clinical trials (Phase 1/2 and Phase 3 combined).	*Figure 3.37: Scatterplot showing the relationship between the number of countries involved and the word count of the risk communication section in Phase 1/2 trials.*	*Figure 3.38: Scatterplot showing the relationship between the number of countries involved and the word count of the risk communication section in Phase 3 trials.*

H1f: Multinational trials are more likely to include standardized or visual display elements compared to trials with a smaller overall number of countries involved.

- A linear regression was conducted using a combined "display element score" (ranging from 0 to 3) as dependent variable.
- In Phase 1/2 trials (n = 19), a slight positive trend was observed between the number of countries involved (mean = 3.58) and the number of display element types included (mean = 1.16), though the association was not statistically significant (slope = 0.076; $R^2 = 0.056$; p = 0.331).
- In Phase 3 trials (n = 24), where the number of countries was generally higher (mean = 10.67), the average number of display element types was also higher (mean = 1.46), but no meaningful association with the number of countries was detected (slope = –0.010; $R^2 = 0.004$; p = 0.771).

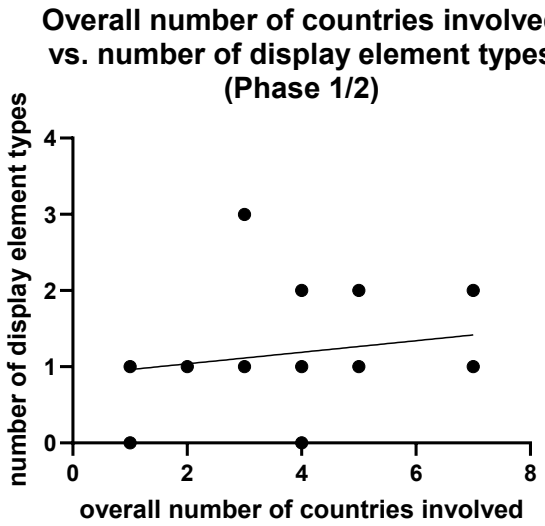

Figure 3.39: Relationship between number of countries involved and display element use in Phase 1/2 trials. Scatter plot with linear regression line showing a non-significant positive trend between the number of countries involved and the number of display element types included in ICFs (slope = 0.076; R^2 = 0.056; p = 0.331; n = 19).

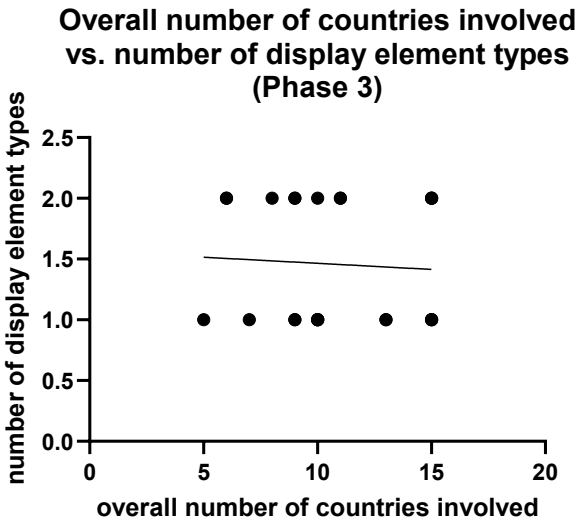

Figure 3.40: Relationship between the number of countries involved and display element use in Phase 3 trials. No association was observed between the number of countries and the number of display element types in ICFs (slope = −0.010; R^2 = 0.004; p = 0.771; n = 24).

H1g: Phase 3 clinical trials are more likely to be multicentric, involving a higher number of countries, compared to Phase 1 trials.

- An unpaired t-test was conducted. The results revealed a highly significant difference in the number of countries involved between trial phases (t(41) = 8.314, p < 0.0001). On average, Phase 3 trials included 10.67 countries, while Phase 1/2 trials involved only 3.58 countries, with a mean difference of 7.09 countries (95% CI: 5.37 to 8.81). The effect size, expressed as η^2 (eta squared), was 0.6277, indicating a strong effect. These findings confirm the hypothesis that later-phase trials are substantially more multicentric in nature.

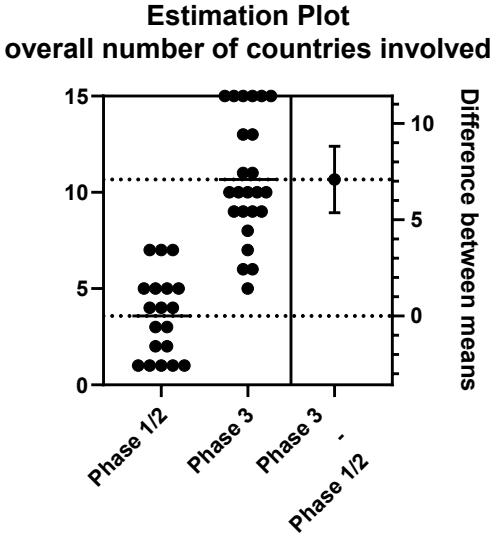

Figure 3.41: Overall number of countries involved in Phase 1/2 versus Phase 3 clinical trials. Each dot represents one clinical trial.

Statistical summary (Phase 1;2 / Phase 3)

- Mean: 3.58 / 10.67
- SD: 1.91 / 2.32
- n: 19 / 24
- p < 0.0001 (unpaired t-test, two-tailed)

3.2.3. Descriptive Results of Experiment 1 (Non-Hypothesis-Driven Data):

3.2.3.1. Risk categories across phases (Phase 1/2 vs Phase 3):

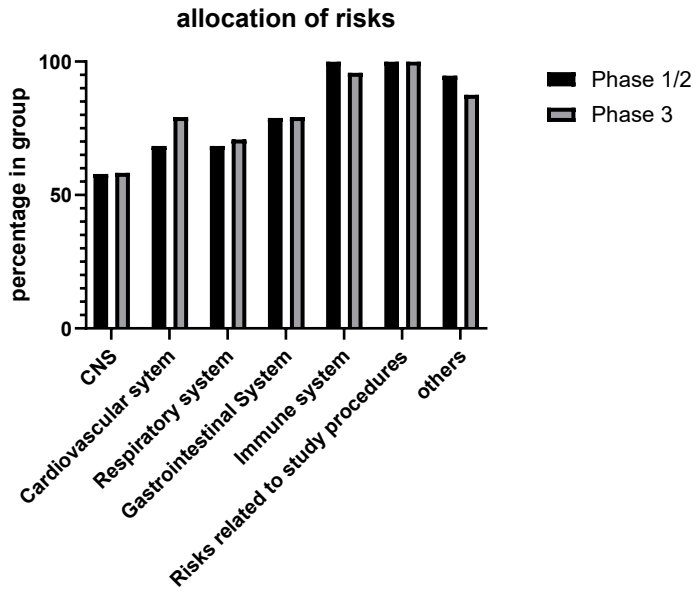

Figure 3.42: Allocation of risk categories in informed consent forms (ICFs) for Phase 1/2 and Phase 3 trials. Bars represent the percentage of studies in each phase that mention risks related to the respective system or domain. Categories reflect etiological classification (e.g., immunologically triggered symptoms were attributed to "immune system" risks, regardless of organ involvement).

To provide a descriptive overview of the types of risks mentioned in the informed consent forms, risk categories were coded and compared between trial phases. Across both Phase 1/2 and Phase 3 trials, the most frequently mentioned risks were those related to the immune system and study procedures, each occurring in nearly all ICFs. Other commonly reported categories included gastrointestinal, respiratory, and cardiovascular risks, with minor differences between the trial phases. Risks related to the central nervous system (CNS) and other less specific categories were present in roughly equal proportions across both groups. Overall, the distribution of risk types appeared broadly similar, with no major qualitative differences between phases.

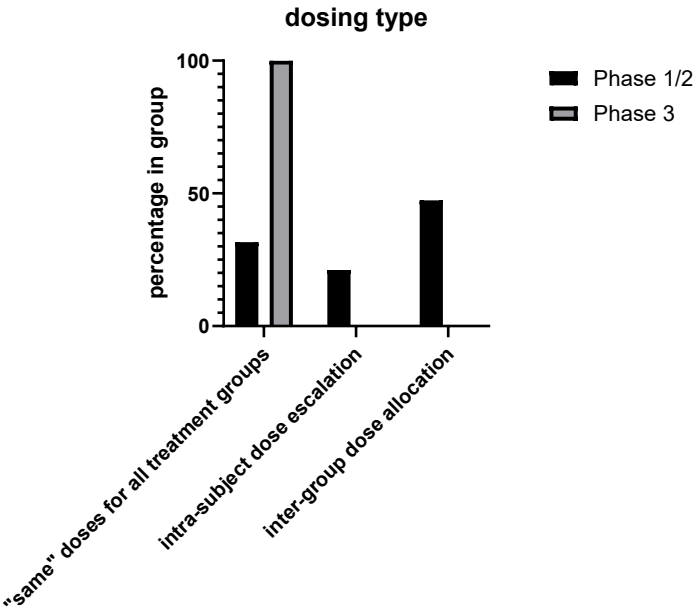

Figure 3.43: Distribution of dosing strategies across trial phases. Phase 1/2 trials employed intra-subject dose escalation and inter-group dose allocation more frequently. In contrast, all Phase 3 trials applied uniform dosing across groups.

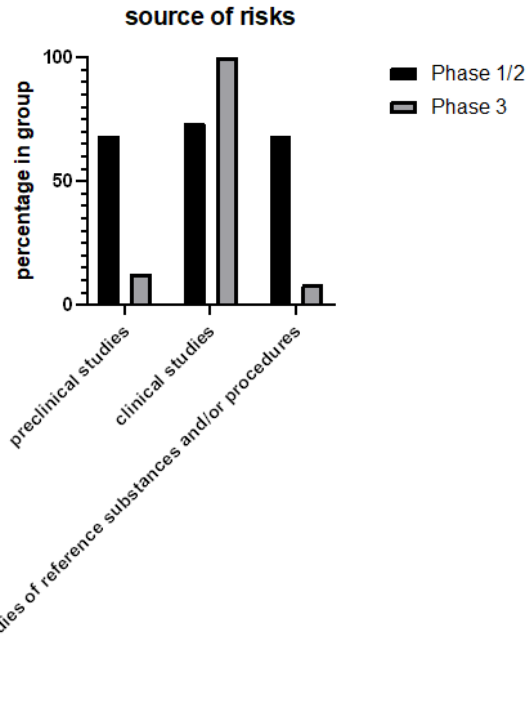

Figure 3.44: Distribution of risk sources in Phase 1/2 and Phase 3 trials. Risks in Phase 1/2 trials were more frequently attributed to preclinical studies and reference substances or procedures, whereas risks in Phase 3 trials were almost exclusively related to clinical studies.

3.2.3.2. AT-DE Comparison:

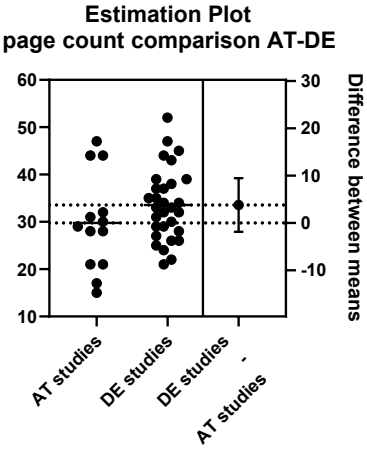

Figure 3.45: Estimation plot comparing page counts between Austrian and German ICFs. While the average page count was higher in DE studies, the difference was not statistically significant (p = 0.183). Shown are individual study values, group means, and 95% confidence interval of the mean difference.

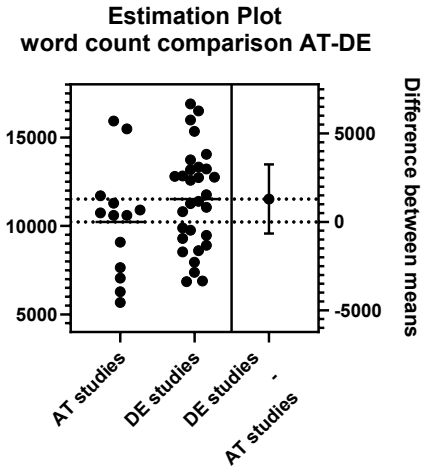

Figure 3.46: Estimation plot comparing word counts between Austrian and German ICFs. No significant difference in word count was found (p = 0.188).

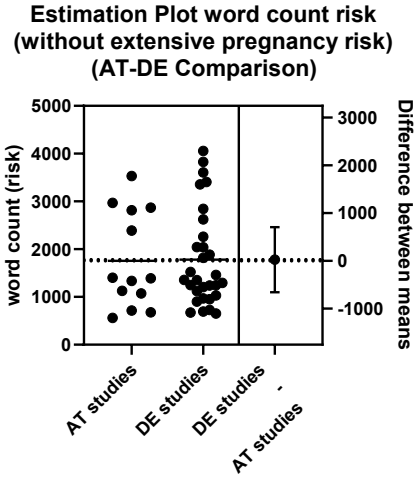

Figure 3.47: Comparison of the number of words dedicated to the risk description in SIS/ICFs from Austrian (AT) and German (DE) clinical trials. No significant difference was observed between both groups.

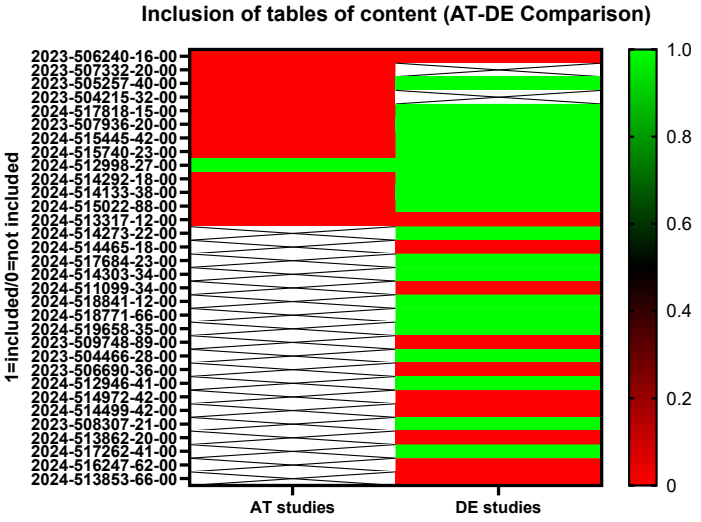

Figure 3.48: Comparison of the inclusion of a table of contents in SIS/ICFs from Austrian (AT) and German (DE) clinical trials. A Mann–Whitney U test revealed a significantly higher frequency of tables of contents in DE documents (U = 86.5, p = 0.0009, two-tailed). The Hodges–Lehmann estimate of the median difference was 1.0, indicating a systematic structural difference between national templates.

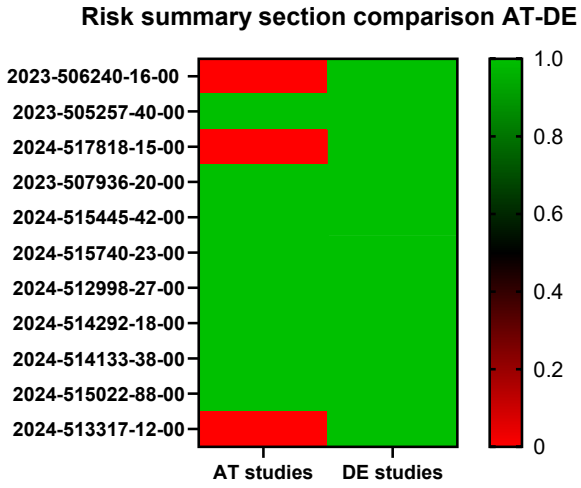

Figure 3.49: Heatmap showing presence (green) or absence (red) of a structured risk summary section in AT and DE versions from ICFs of the same studies. While DE studies included such sections more frequently (8 vs 11), this difference did not reach statistical significance, possibly due to the limited sample size (McNemar's test, p = 0.083).

Page and word count:

To investigate regional differences in information content and structure, Austrian (AT) and German (DE) ICFs were compared with regard to their word and page counts. Mean page count was slightly higher in DE studies (33.57 pages) compared to AT studies (29.77 pages), although the difference was not statistically significant (t = 1.356, p = 0.1826; 95% CI: −1.86 to 9.45). Similarly, the word count was higher in DE studies (11,525 words vs. 10,229 words), but again, this difference did not reach statistical significance (t = 1.339, p = 0.1880; 95% CI: −658 to 3,249). In both comparisons, estimation plots showed a high degree of overlap, and R^2 values were low, suggesting small effect sizes.

Risk Summary Section:
In 8/11 Austrian ICFs and 11/11 German ICFs, a structured risk summary section was present. McNemar's test indicated that this difference was not statistically significant ($p = 0.083$, asymptotic, without Yates' continuity correction), though a trend-level difference may be noted. A heatmap was generated to visually display these within-study differences.

Pregnancy/Contraception Section Placement:
For all 11 Austrian–German ICF pairs referring to the same clinical trials, the presence of information on pregnancy and contraception exclusively in the exclusion criteria section (Code 3 in the matrix = "Who Is Not Allowed to Participate in This Clinical Trial?") was assessed using McNemar's test. In 6 of 11 cases (54.5 %), only the German ICF contained such a placement, while in none of the pairs was this exclusive to the Austrian ICF. This asymmetrical distribution was statistically significant (exact McNemar's test, $p = 0.031$), indicating that German ICFs were more likely to include pregnancy/contraception-related information in the exclusion criteria section compared to their Austrian counterparts, which more commonly used the general "pregnancy/ fertility" sections.

3.3. Experiment 2

3.3.1. Main Hypothesis:

H2: SIS/ICFs released after the enforcement of the GDPR/ General Data Protection Regulation (2018) and after introduction of the CTR/ Clinical Trials Regulation are significantly longer and contain more extensive data protection information than those released before.

- Informed Consent Forms (ICFs) released after the enforcement of the General Data Protection Regulation (GDPR) were significantly longer than those from the pre-GDPR period (2011–2014). This was reflected both in page counts (mean difference: 18.33 pages, $p < 0.0001$) and total word counts (mean difference: 4874 words, $p < 0.0001$).
- Similarly, the total Data protection text was substantially longer in the post-GDPR group, with a mean increase of 643 words ($p = 0.0062$). However, when normalized to total document length, the relative proportion of the total data protection text did not significantly differ between time periods (mean proportion ~13.7% in both groups, $p = 0.9995$). This suggests that while absolute content increased, its share within the overall ICF remained stable.
- For the dedicated data protection section category alone, similar results can be viewed below.
- No significant difference was found in the word count of consent forms containing data protection content between the 2011–2014 and 2022–2024 groups (mean difference: −51.1 words, $p = 0.376$).

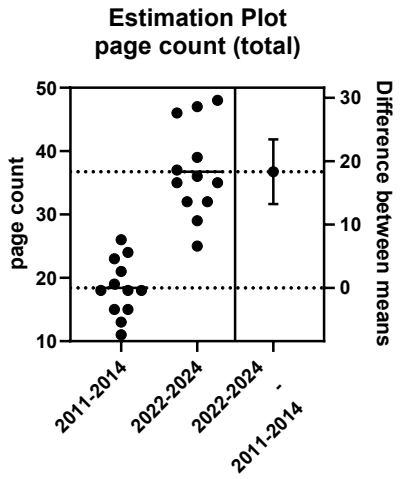

Figure 3.50: Estimation plot comparing total page counts of ICFs released before (2011–2014) and after (2022–2024) GDPR enforcement. Post-GDPR ICFs were significantly longer in page count ($p < 0.0001$, unpaired t-test).

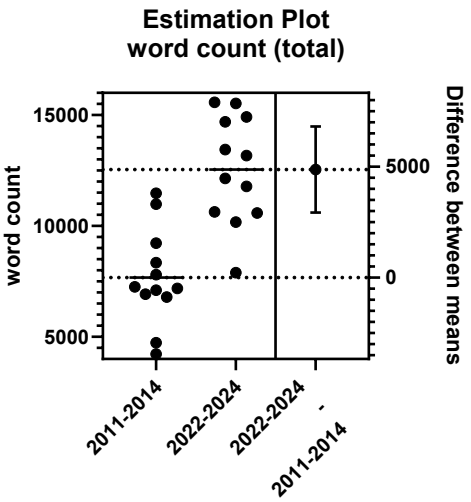

Figure 3.51: Estimation plot showing total word counts of ICFs by issuance period. Word counts were significantly higher in the post-GDPR group ($p < 0.0001$).

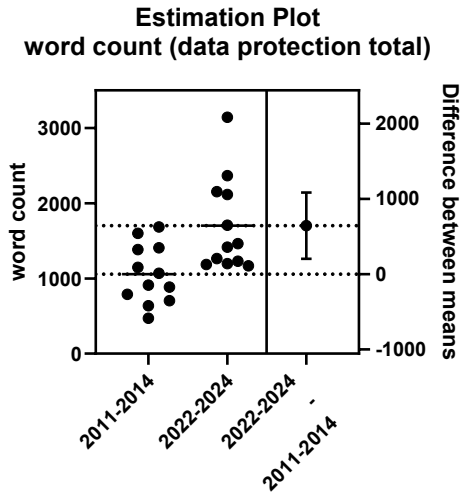

Figure 3.52: Estimation plot comparing total word counts of the data protection sections. ICFs released after GDPR enforcement included significantly more extensive data protection content ($p = 0.0062$).

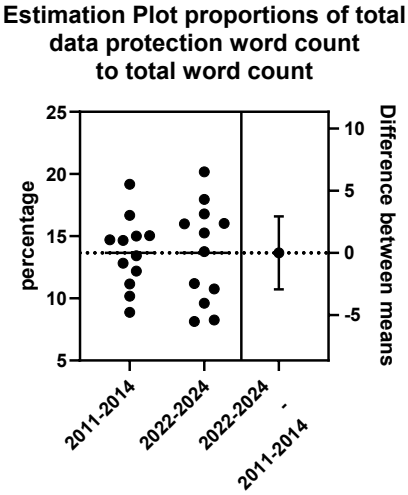

Figure 3.53: Estimation plot of total data protection word count as a proportion of total ICF word count. No significant difference in proportional representation was found between the groups ($p = 0.9995$).

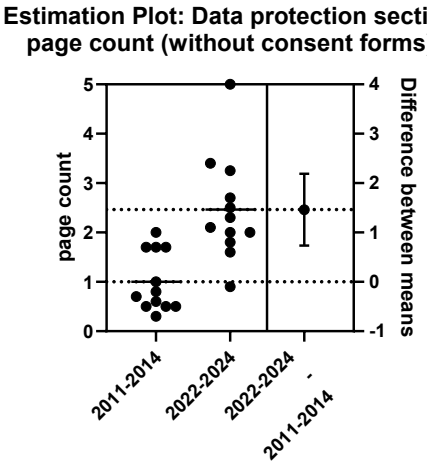

Figure 3.54: Comparison of page counts of the data protection section (excluding consent forms) in participant information documents from two time periods. An unpaired two-tailed t-test was conducted. The average page count significantly increased from 1.00 to 2.46 pages (mean difference: 1.463 ± 0.3504, $p = 0.0004$, 95% CI: 0.7358 to 2.189). This result indicates a marked expansion of the data protection content in more recent documents. Each dot represents one study.

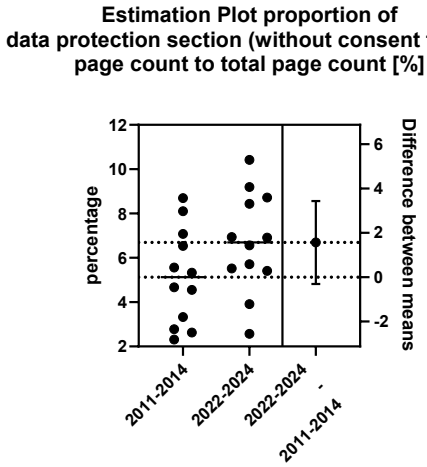

Figure 3.55: Proportion of the data protection section (without consent forms) relative to total document length (in %) for clinical trial documents from 2011–2014 and 2022–2024. While the average proportion was higher in the 2022–2024 group (mean = 6.69%) compared to the 2011–2014 group (mean = 5.13%), the difference was not statistically significant (unpaired two-tailed t-test, $p = 0.0974$, 95% CI [–0.31, 3.43], $n = 12$ per group).

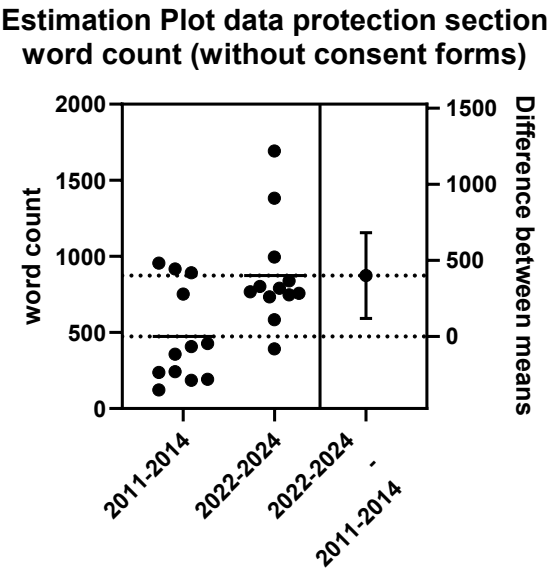

Figure 3.56: Word count of data protection sections (excluding consent forms) in Phase 1/2 (2011–2014) and Phase 3 (2022–2024) ICFs. An unpaired t-test revealed a significantly higher word count in the data protection sections of ICFs from 2022–2024 (mean = 873.7 words) compared to those from 2011–2014 (mean = 474.3 words), t(22) = 2.943, p = 0.0075. The mean difference was 399.3 words (±135.7 SEM), with a 95% CI of 117.9 to 680.7.

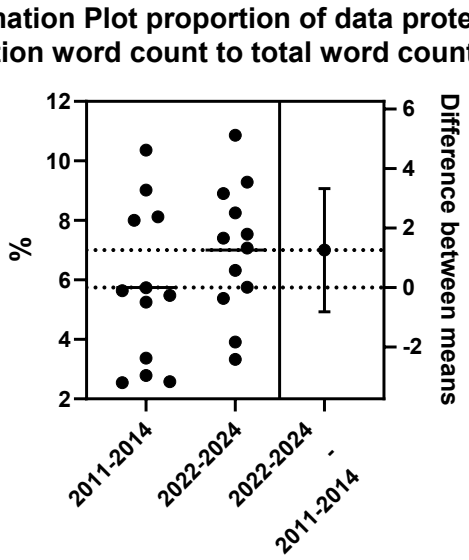

Figure 3.57: Estimation plot comparing informed consent forms (ICFs) from two time periods (2011–2014 and 2022–2024) in terms of the proportion of total word count dedicated to the data protection section (without consent forms). Although the mean proportion increased from 5.742% in the earlier group to 7.000% in the later group, the difference was not statistically significant (mean difference = 1.258 ± 0.997; 95% CI: −0.809 to 3.325; p = 0.220; unpaired two-tailed t-test, n = 12 per group).

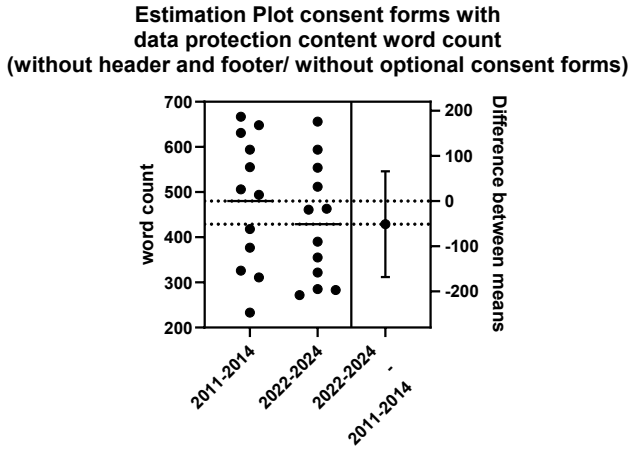

Figure 3.58: Estimation plot showing the word count of consent forms containing data protection content (excluding header/footer and optional forms) between the 2011–2014 and 2022–2024 groups. The mean word count was 480.0 for the earlier group and 428.9 for the latter group. The unpaired two-tailed t-test indicated no significant difference between the groups (p = 0.3760). The mean difference was −51.08 words (± 56.53 SEM), with a 95% confidence interval of −168.3 to 66.15. Each dot represents one document.

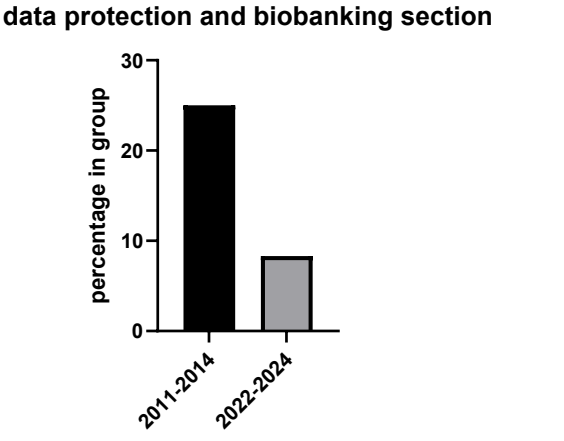

Figure 3.59: Proportion of informed consent forms (ICFs) in which the data protection section was combined with the biobanking section, by time period. The chart shows that in the period 2011–2014, 25% of ICFs combined both sections, while in 2022–2024 this applied to only 8.3% of cases, indicating a trend toward clearer separation of these topics in more recent documents

3.3.2. Secondary Hypotheses:

H2a: SIS/ICFs released after the GDPR are more likely to contain explicit references like "right to erasure" or data retention duration, than those released before.

- A chi-square test was performed on the total number of specific data protection references in the informed consent forms (ICFs). The total number of references refers to a selected subset of representative data protection elements, not an exhaustive list. ICFs from 2022–2024 contained substantially more explicit references (e.g., GDPR, right to erasure, data retention) than those from 2011–2014 (82 vs. 52 out of a possible 96). This difference was statistically significant ($\chi^2(1) = 3.99$, $p = 0.0458$), supporting Hypothesis H2a and indicating broader and more explicit data-protection coverage in post-GDPR ICFs. References to the GDPR appeared in 100% of recent ICFs versus 0% historically, and the right to erasure likewise rose from 0% to 100%. Mentions of data transfer outside the EU increased from 41.7% to 100%, and data-retention duration from 41.7% to 83.3%. Digital elements rose from 66.7% to 100%. Third-party use of data remained universally reported (100% in both cohorts). Citations to national law shifted: references to the Austrian Data Protection Act 2000 fell from 91.7% to 0%, whereas references to the Austrian Medicines Act increased slightly (91.7% → 100%). (see Figure 3.60)
- Here, a "reference" means that a predefined data-protection element is explicitly mentioned at least once in the ICF; multiple repetitions within the same ICF are counted once (presence/absence).
- Additional special data retention duration rules were only present in two ICFs from the 2022–2024 time period and were not included in the statistical analysis for this hypothesis.

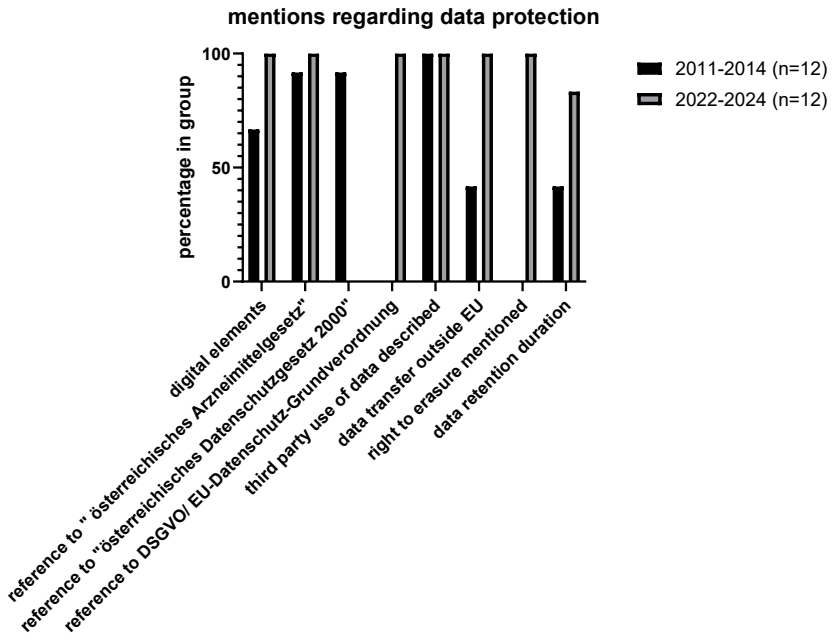

Figure 3.60: Percentage of informed consent forms (ICFs) including specific data protection references across two time periods. Each bar indicates the proportion of ICFs mentioning the respective element. A chi-square test comparing the total number of references revealed a significant increase in the later cohort ($\chi^2(1) = 3.99$, $p = 0.0458$).

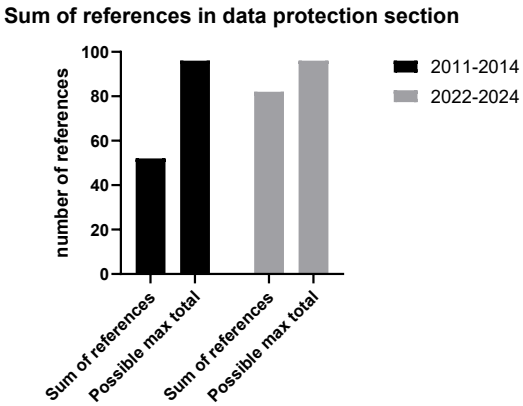

Figure 3.61: Total number of specific references in the data protection sections of informed consent forms (ICFs) from two time periods (2011–2014 and 2022–2024), displayed in relation to the respective maximum number of possible items in each group. Within each cohort, two bars are plotted: the theoretical maximum (12 ICFs × 8 elements = 96) and the observed total (sum of present elements, counted once per ICF per element). A higher observed total and a smaller gap to 96 indicate more comprehensive coverage of relevant data protection topics in the recent cohort.

H2b: SIS/ICFs released after the GDPR are more likely to include separate, dedicated data protection and biobanking consent forms and/or additional box selection.

- The inclusion of separate consent forms or additional box selections for data protection and biobanking was more frequent in ICFs released after the GDPR (2022–2024: 70.8%) compared to those released before (2011–2014: 41.7%). However, this difference did not reach statistical significance ($\chi^2(1) = 1.172$, $p = 0.2791$, two-sided).
- Both data protection and biobanking were more frequently addressed via additional consent mechanisms in ICFs from 2022–2024 than in those from 2011–2014. While the descriptive increase was visible for both categories, statistical analysis was performed on the combined occurrences of additional data protection and biobanking consent elements, due to limited individual counts.

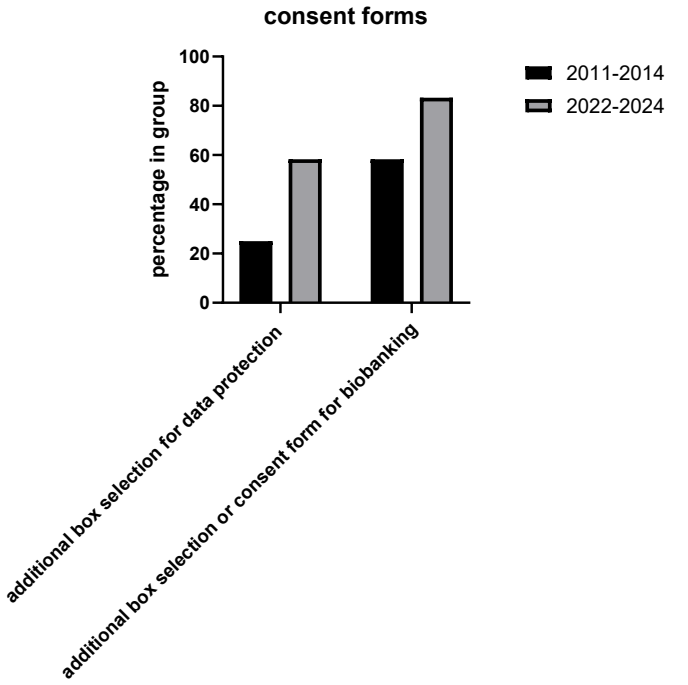

Figure 3.62: The chart shows the proportion of ICFs in each time group that included either a dedicated data protection selection or a biobanking consent form or selection. While both features increased in the 2022–2024 group, statistical analysis was performed on the combined counts only (see Figure 3.63). Notably, additional consent for data protection was always in the form of an optional selection box; no separate data protection consent forms were found. In contrast, biobanking was addressed either via separate forms or selection boxes.

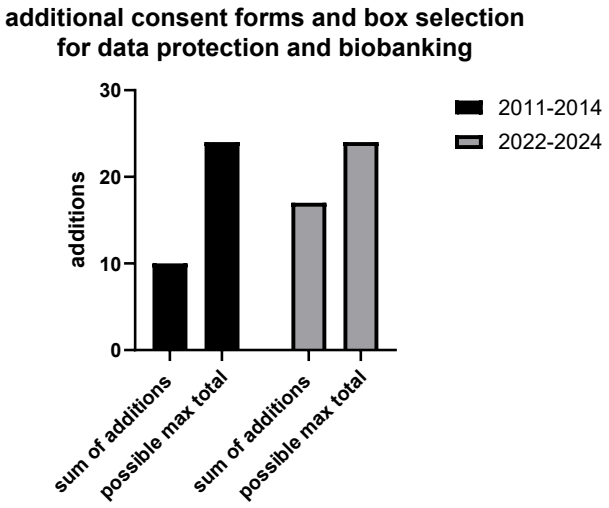

Figure 3.63: Combined frequency of additional consent forms and box selection for data protection and biobanking. The bar graph displays the absolute number of additions and the maximum possible total per group. An "addition" is defined as the presence of either a separate consent form or a selection box. Each domain (data protection, biobanking) contributes at most one addition per ICF. Thus, for each group, the maximum possible total is 24 (12 ICFs × 2 domains). The increase in the 2022–2024 group was not statistically significant (Chi-square test, p = 0.2791).

H2c: Planned participant count is positively associated with the length of the risk communication section.

- Simple linear regressions were conducted separately for ICFs released before (2011–2014) and after (2022–2024) the GDPR enforcement (only the risk word count without extensive pregnancy and/or contraception risk information was used for the analysis).
- For ICFs from 2011–2014, no significant association was found between planned participant count and risk word count (slope = –0.127, $p = 0.574$, $R^2 = 0.033$). This remained non-significant after exclusion of statistical outliers (slope = 0,334, $p = 0.615$, $R^2 = 0.0293$).
- For ICFs from 2022–2024, although the regression slope was positive (slope = 2.04), the association did not reach statistical significance ($p = 0.109$, $R^2 = 0.237$).

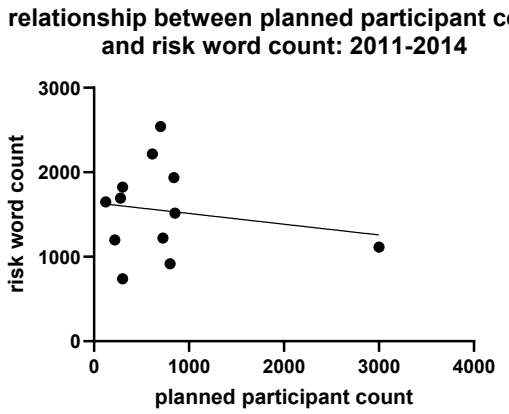

Figure 3.64: Scatterplot with regression line showing the relationship between planned participant count and risk section word count in ICFs from 2011–2014. No significant association was found (p = 0.574).

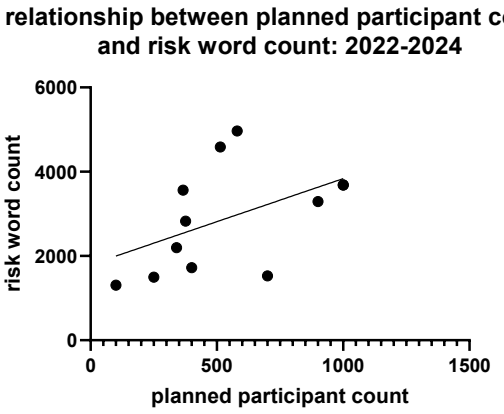

Figure 3.65: Scatterplot with regression line showing the relationship between planned participant count and risk section word count in ICFs from 2022–2024. Although the slope was positive, the relationship was not statistically significant (p = 0.109).

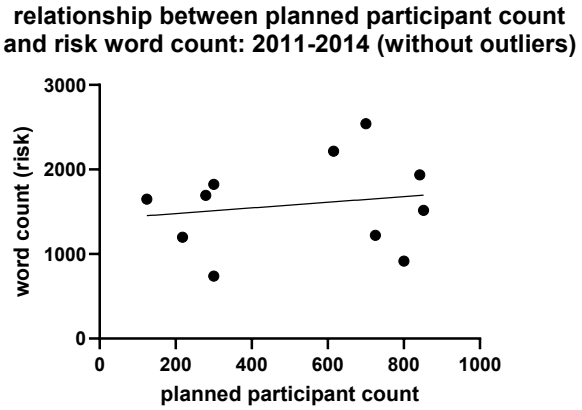

Figure 3.66: Same as Figure 3.64, but excluding outliers. The relationship remained non-significant (p = 0.615).

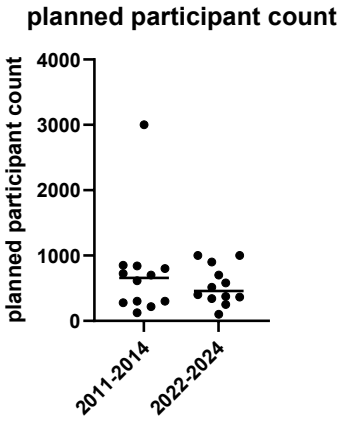

Figure 3.67: Scatterplot with means showing the planned participant counts in both groups

H2d: The presence of biobanking content is positively associated with total ICF word count.

- Informed consent forms (ICFs) that included biobanking content were significantly longer than those without. The mean word count for ICFs with biobanking content was 10,637, compared to 6,409 for ICFs without biobanking content. This difference was statistically significant (unpaired t-test, p = 0.0378, t(22) = 2.210), with a 95% confidence interval for the difference ranging from 260 to 8,197 words. The effect size (η^2) was 0.1816, indicating a moderate effect.
- It should be noted that only three ICFs lacked biobanking content, two of which were from the earlier time period (2011–2014), which generally contained shorter documents overall. Therefore, the observed difference in word count may partly reflect the influence of time period rather than biobanking content alone.

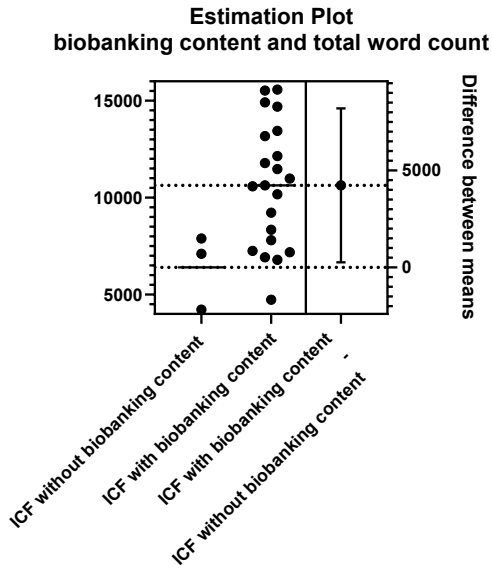

Figure 3.68: Estimation plot comparing total word count of ICFs with and without biobanking content. ICFs, including biobanking content, had significantly higher word counts than those without (unpaired t-test, p = 0.0378). Note that two of the three ICFs without biobanking content originated from the earlier time period (2011–2014), which was generally associated with shorter ICFs. The difference might therefore partially reflect temporal changes rather than biobanking content alone.

H2e: SIS/ICFs that include biobanking content are more likely to have a higher number of additional separate signature forms.

- We compared the number of additional consent forms in ICFs with and without biobanking content using a Mann-Whitney U test. There was no statistically significant difference in the number of additional consent forms between ICFs with biobanking content (n = 21) and those without biobanking content (n = 3), U = 22.50, p = 0.5464 (two-tailed). The median number of additional consent forms was 0 in both groups.

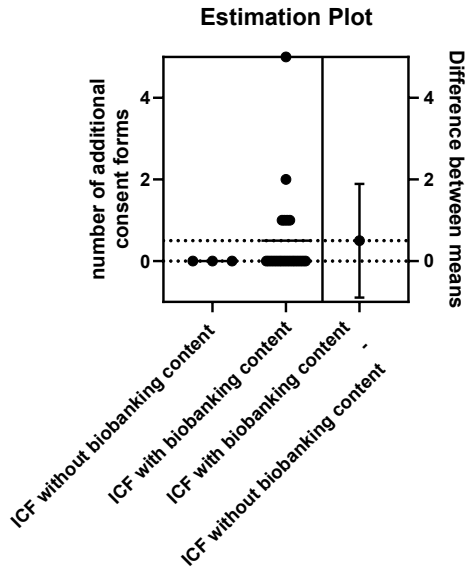

Figure 3.69: Estimation plot of number of additional consent forms for ICFs with vs. without biobanking content. ICFs, including biobanking content (n = 21) tended to have a higher number of additional consent forms (e.g., separate signature pages) compared to those without biobanking content (n = 3), but this difference was not statistically significant.

H2f: The level of detail in biobanking sections (e.g., storage duration, reuse scope, sample coding, ...) correlates with the total word count of the ICF.

- For the construction of a detail score, the following attributes of each ICF were evaluated:
  - Biobanking as part of the study
  - Dedicated biobanking consent form with separate signature approval or additional box selection
  - Named storage locations mentioned
  - Re-use scope described
  - Third-party use of biological samples described
  - Sample coding described
  - Coding of sample data explicitly described
  - ICF explicitly states destruction of leftover samples
- A biobanking complexity score was created by counting the number of included aspects (In the visualizations below, additional aspects are shown that were not evaluated for the complexity score). Linear regression analysis revealed a statistically significant positive correlation between the biobanking complexity score and total ICF word count in both study periods (The separation was conducted to prevent confounding effects). For ICFs from 2011–2014, a moderate to strong correlation was observed ($r^2 = 0.5601$, $p = 0.0051$), whereas ICFs from 2022–2024 showed a weaker but still significant association ($r^2 = 0.3552$, $p = 0.0408$). These results suggest that more extensive and detailed biobanking descriptions tend to appear in longer ICFs.

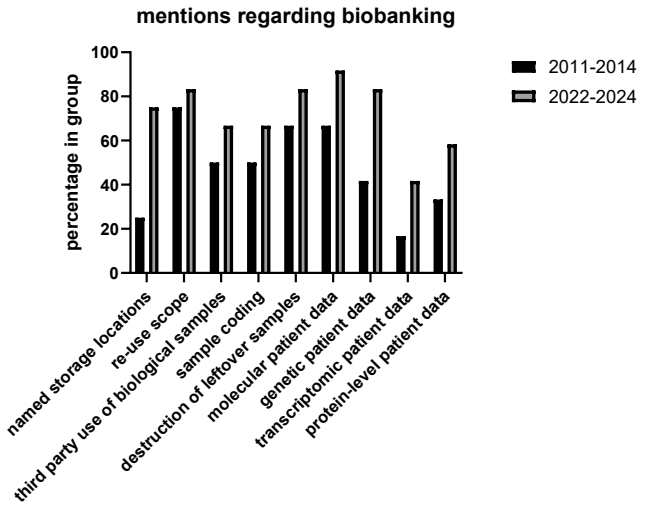

Figure 3.70: Percentage of ICFs from 2011–2014 and 2022–2024 that mentioned specific biobanking details

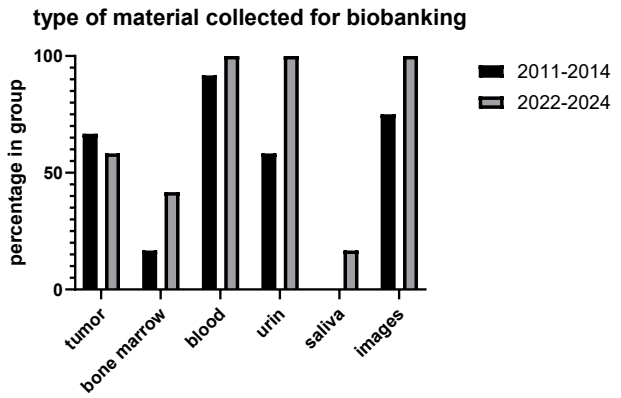

Figure 3.71: Types of biological material collected for biobanking, as described in ICFs from both study periods.

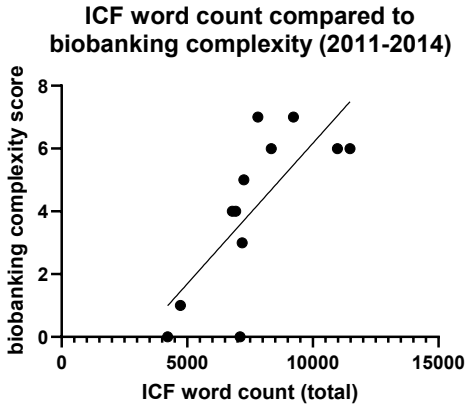

Figure 3.72: Correlation between total word count and biobanking complexity score in ICFs from 2011–2014. A significant positive relationship was observed ($r^2 = 0.5601$, $p = 0.0051$).

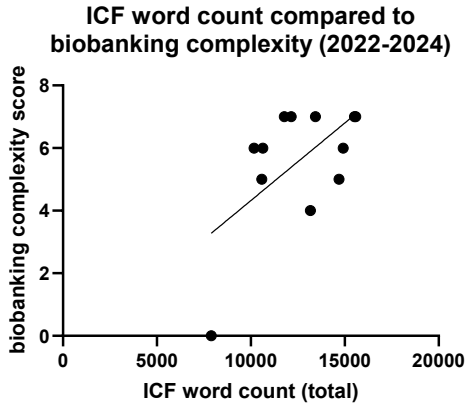

Figure 3.73: Correlation between total word count and biobanking complexity score in ICFs from 2022–2024. The association was weaker but statistically significant ($r^2 = 0.3552$, $p = 0.0408$).

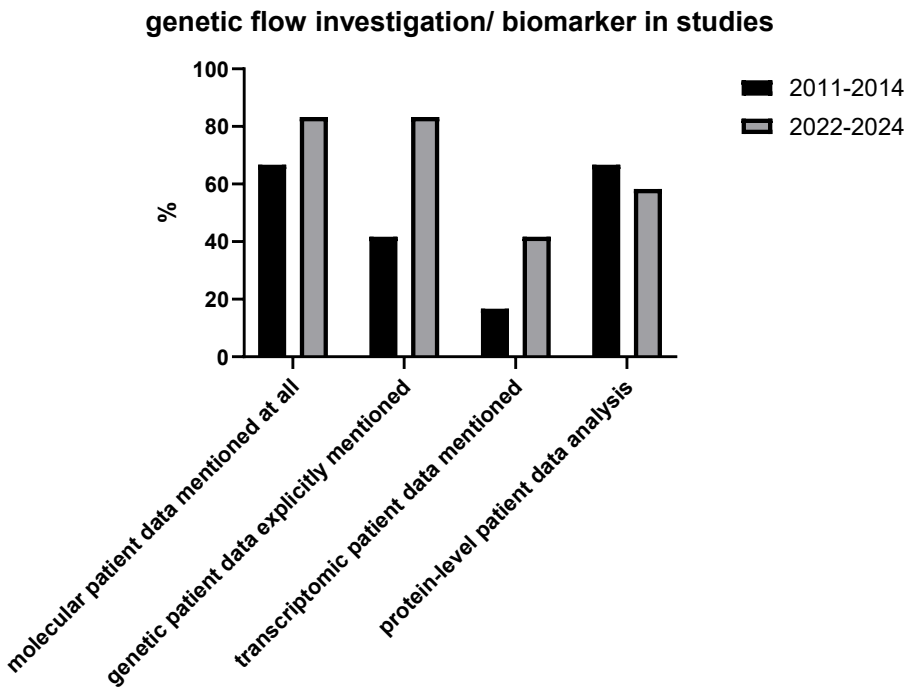

Figure 3.74: Proportion of studies involving the collection of molecular or biomarker-related patient data. The figure shows the percentage of informed consent forms (ICFs) from 2011–2014 and 2022–2024 that included the collection of different types of molecular patient data, such as general molecular data, genetic data, transcriptomic data, and protein-level analyses. Transcriptomic analyses were generally less common. A slight increase in molecular data is observed in the 2022–2024 group.

H2g: The use of dedicated headings for biobanking content is associated with longer SIS/ICFs.

- 2011–2014 group: An unpaired t-test comparing the total word count of ICFs with a dedicated biobanking section (n = 7) to those without such a section (n = 5) showed no significant difference (p = 0.1939, two-tailed). The mean word count for ICFs with a dedicated biobanking heading was 8374, and for ICFs without it was 6690. The difference between means was 1684 ± 1209 words (95% CI: −1011 to 4379). The effect size (R^2) was 0.1624.
- 2022–2024 group: An unpaired t-test comparing ICFs with a dedicated biobanking section (n = 9) to those without (n = 3) also revealed no significant difference (p = 0.3507, two-tailed). The mean word count for ICFs with the section was 11354, and for those without it was 12943. The difference between means was −1589 ± 1623 words (95% CI: −5204 to 2027). The effect size (R^2) was 0.0875.
- The separation of both groups was conducted to prevent confounding effects.

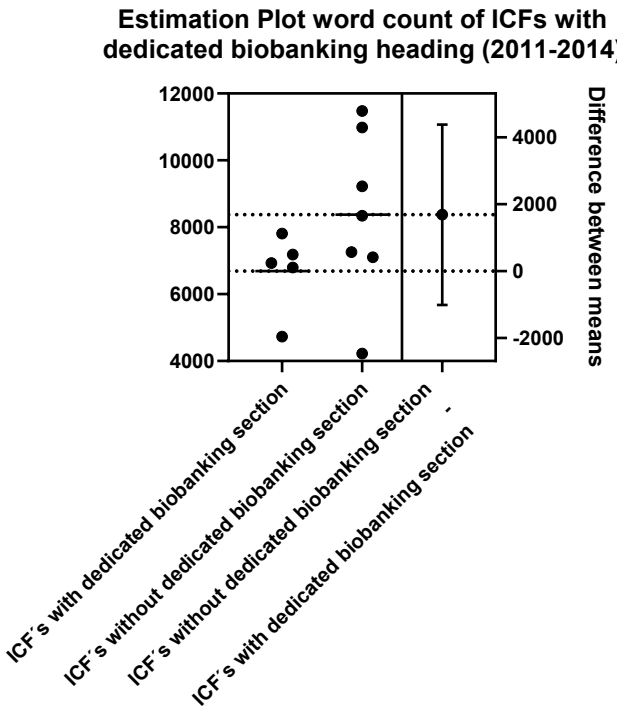

Figure 3.75: Estimation plot comparing the total word count of ICFs with and without a dedicated biobanking heading in the 2011–2014 group. ICFs with a dedicated heading (n = 7) were descriptively longer, but the difference was not statistically significant (p = 0.1939, unpaired t-test).

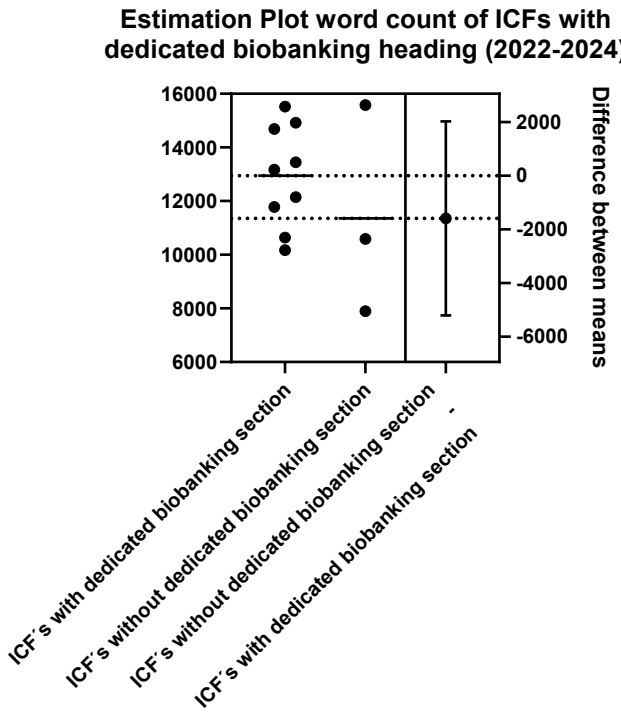

Figure 3.76: Estimation plot comparing the total word count of ICFs with and without a dedicated biobanking heading in the 2022–2024 group. ICFs with a dedicated heading (n = 3) were descriptively shorter, but again the difference was not statistically significant (p = 0.3507, unpaired t-test)

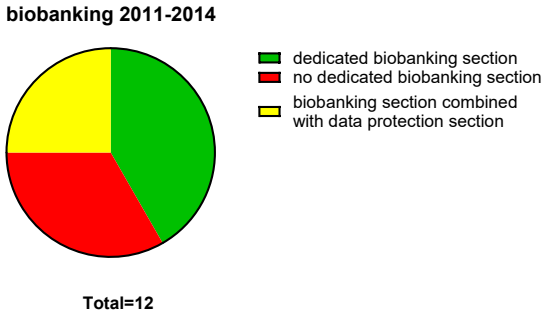

Figure 3.77: Presence and structure of biobanking sections in ICFs from 2011–2014. The pie chart displays the distribution of biobanking-related content across 12 ICFs. 5 included a dedicated biobanking section (green), 4 did not have a dedicated biobanking section at all (red), and 3 embedded biobanking content within the data protection section (yellow).

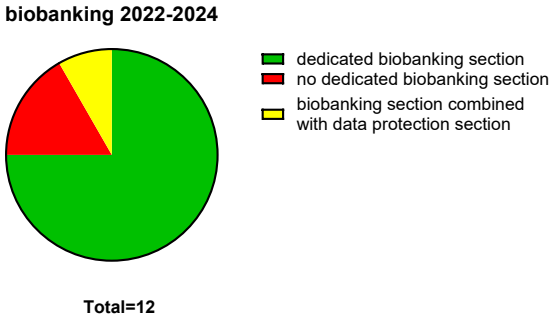

Figure 3.78: Presence and structure of biobanking sections in ICFs from 2022–2024. The updated distribution among 12 ICFs shows a shift toward clearer structuring: 9 included a dedicated biobanking section (green), 2 did not have a dedicated biobanking section at all (red), and 1 ICF embedded it in the data protection section (yellow).

H2h: SIS/ICFs after 2018 have a significantly higher Biobanking word count.

- To test the hypothesis that informed consent forms (ICFs) published after 2018 contain more biobanking-related information, several metrics were compared between forms from 2011–2014 and 2022–2024. A significant increase was found in the absolute biobanking word count excluding consent forms, with a mean of 240.3 words in the 2011–2014 group and 543.6 words in the 2022–2024 group ($p = 0.0151$; 95% CI [64.8, 541.9]; $\eta^2 = 0.24$). In contrast, the relative proportion of biobanking content (excluding consent forms) to total word count did not differ significantly between groups (mean: 2.9% vs. 4.3%; $p = 0.2191$).

- A non-significant trend was also observed in the total biobanking word count (incl. consent forms), which increased from 667.9 to 1164 words (p = 0.1166). The relative proportion of total biobanking-related content within the ICFs showed no significant change (p = 0.6627).
- These results suggest that while biobanking content increased in absolute terms, this growth was not proportionally larger relative to the overall length of ICFs. Moreover, interpretation of the total biobanking word count is limited by structural overlaps with (generally more extensive) data protection sections, where biobanking content is often embedded and not clearly separable.

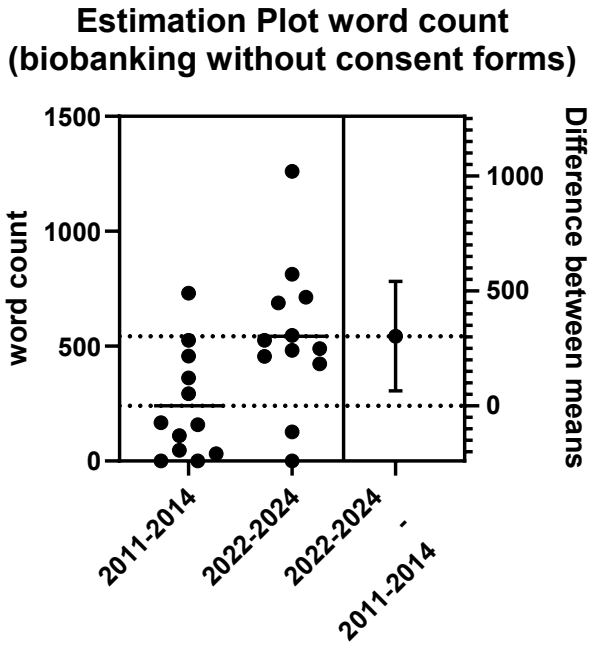

Figure 3.79: Estimation plot comparing the biobanking word count (excluding consent forms) between ICFs from 2011–2014 and 2022–2024. A significant increase in word count was observed in the recent ICFs (p = 0.0151).

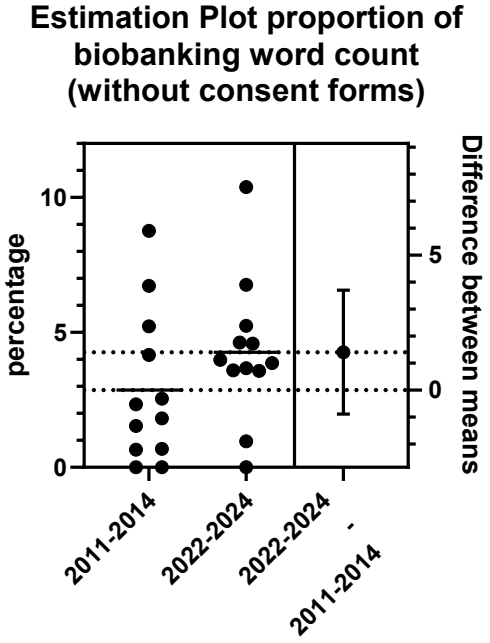

Figure 3.80: Estimation plot comparing the relative proportion of biobanking word count (excluding consent forms) to total word count. No significant difference was detected between the two groups (p = 0.2191).

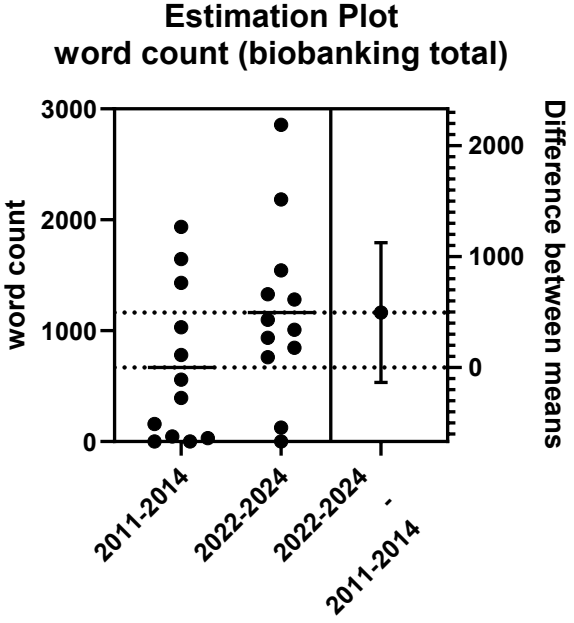

Figure 3.81: Estimation plot of total biobanking word count (including consent forms). Although the mean word count increased in the 2022–2024 group, the difference did not reach significance (p = 0.1166).

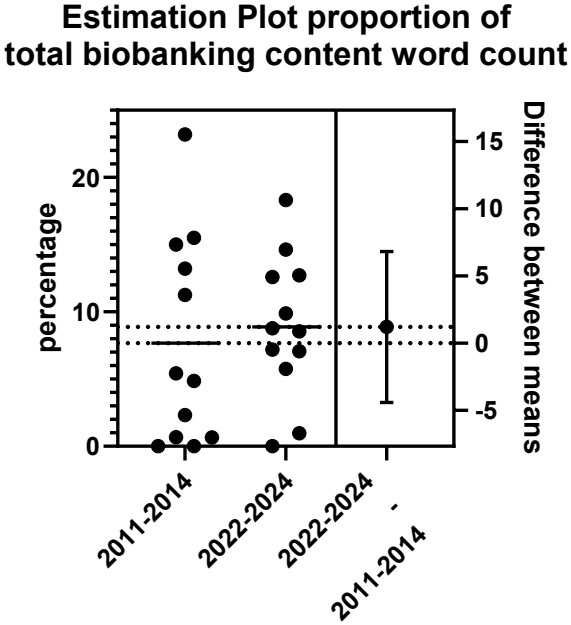

Figure 3.82: Estimation plot showing the proportion of total biobanking-related content relative to overall ICF word count. No significant difference was observed between the two time periods (p = 0.6627).

H2i: Biobanking consent forms have become more common and, when present more extensive after 2018

- To test whether biobanking consent forms have become more prevalent and extensive since 2018, we compared ICFs from two time periods (2011–2014 vs. 2022–2024) across four dimensions:
    - 1. number of biobanking-related consent forms.
    - 2. number of additional biobanking-specific consent forms.
    - 3. word count of all biobanking consent forms.
    - 4. word count of biobanking consent forms that explicitly mention biobanking. (Exclusion of all SIS/ICFs that do not include consent forms with explicit biobanking information)
- There was no statistically significant difference in the number of consent forms with biobanking information ($M_1 = 0.75$ vs. $M_2 = 1.17$, $p = 0.3383$), or in the number of additional biobanking-specific consent forms ($M_1 = 0.33$ vs. $M_2 = 0.42$, $p = 0.8516$). Likewise, the word count of biobanking consent forms did not differ significantly between the two periods ($M_1 = 270.3$ vs. $M_2 = 464.8$, $p = 0.1923$), even when the analysis was restricted to consent forms with explicit biobanking information ($M_1 = 463.3$ vs. $M_2 = 557.8$, $p = 0.5679$).
- None of the differences reached statistical significance, and the effect sizes were consistently small ($R^2 \leq 0.08$). Nevertheless, mean values were consistently higher for the 2022–2024 period.

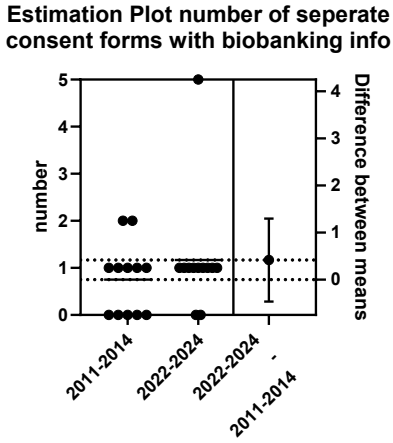

Figure 3.83: Estimation plot: Number of separate consent forms containing biobanking information in ICFs from 2011–2014 and 2022–2024. No significant difference was observed (p = 0.3383).

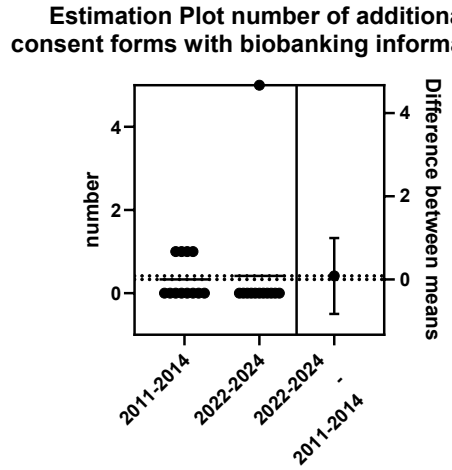

Figure 3.84: Estimation plot: Number of additional biobanking-specific consent forms. No significant difference between time periods (p = 0.8516).

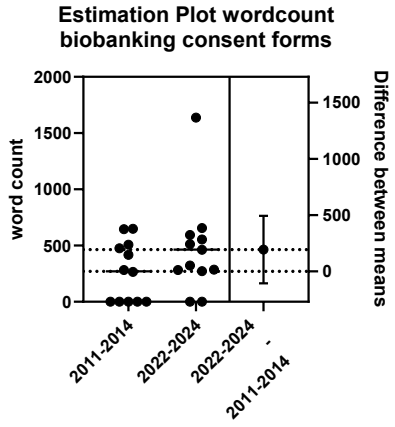

Figure 3.85: Estimation plot: Word count of biobanking consent forms (all forms). Higher mean word counts after 2018, but not statistically significant (p = 0.1923).

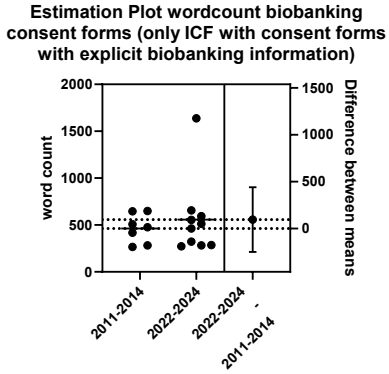

Figure 3.86: Estimation plot: Word count of biobanking consent forms (only ICFs with explicit biobanking info). No significant difference observed (p = 0.5679). (Exclusion of all ICFs that do not include consent forms with explicit biobanking information)

H2j: SIS/ICFs, including flowcharts or visual elements, are shorter in word count.

- A comparison of ICFs with versus without visual elements (e.g., flowcharts) revealed a statistically significant difference in total word count (unpaired t-test, p = 0.0309, two-tailed). The mean word count for ICFs with visual elements was 12931, while ICFs without visualizations had a significantly lower mean word count of 9366 words. The difference in means was 3565 ± 1546, with a 95% confidence interval ranging from -6771 to -359.5. The effect size (eta squared) was 0.1947, suggesting a moderate effect.
- Visualizations were present in only 5 ICFs, compared to 19 ICFs without them. It is important to note that 2 out of the 5 visual ICFs were from the 2011–2014 group, which generally had shorter word counts overall. This may have influenced the result and should be considered when interpreting the outcome.

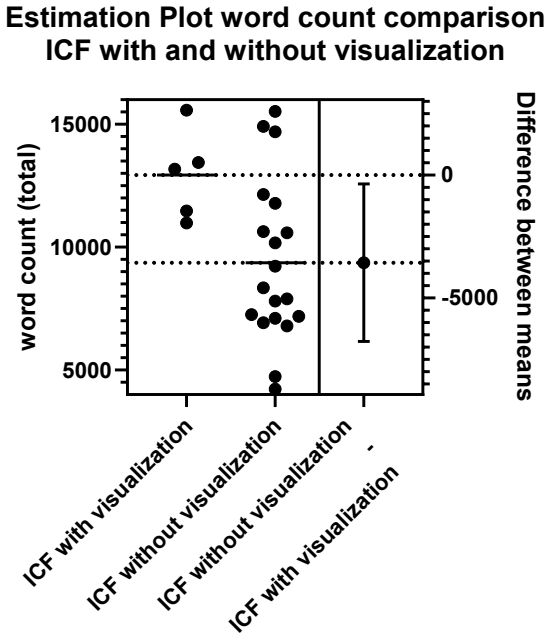

Figure 3.87: Estimation plot comparing the total word count of ICFs with and without visual elements (e.g., flowcharts). ICFs that included visualizations (n = 5) were significantly longer than those without (n = 19). Mean difference = –3565 words, 95% CI [–6771, –359.5], p = 0.0309 (unpaired two-tailed t-test). While this suggests an association between visual content and longer ICFs, the findings should be interpreted cautiously due to unequal group sizes and confounding by study year.

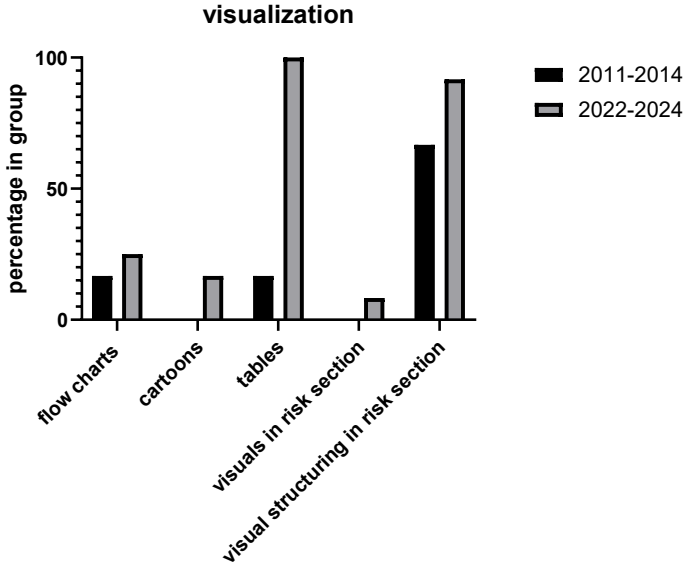

Figure 3.88: Types of visual elements in ICFs from two time periods (2011–2014 vs. 2022–2024). Bar graph showing the proportion of ICFs using different forms of visual representation. Only the categories: flow charts, cartoons, and visuals in risk section, were used as criteria for classifying an ICF as "with visualization" in Figure 3.87. The categories visual structuring in risk section and tables were excluded from that classification.

3.3.3. Descriptive Results of Experiment 2 (Non-Hypothesis-Driven Data):

Risk section data:

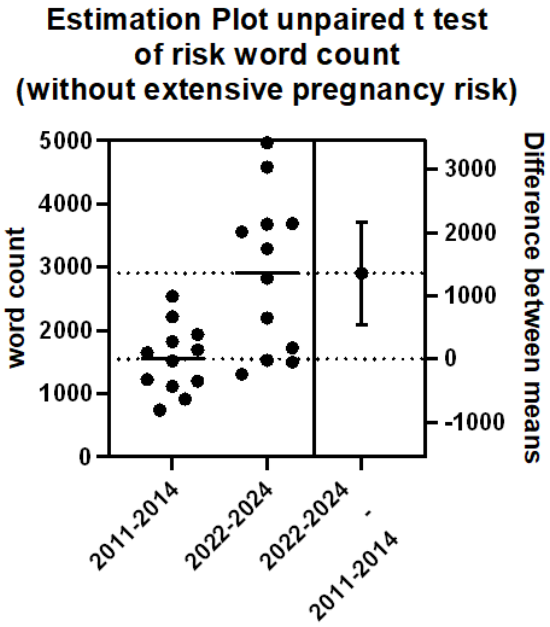

Figure 3.89: Comparison of the word count of the risk section (excluding extensive pregnancy-related content) in SIS/ICFs from 2011–2014 and 2022–2024 (t(22) = 3.455, p = 0.0023). The newer SIS/ICFs contained an average of 2,904 risk-related words compared to 1,547 words in the earlier group. The mean difference was 1,358 words (± 393 SEM, 95% CI: 543 to 2,173). A large effect size was observed (η^2 = 0.3518)

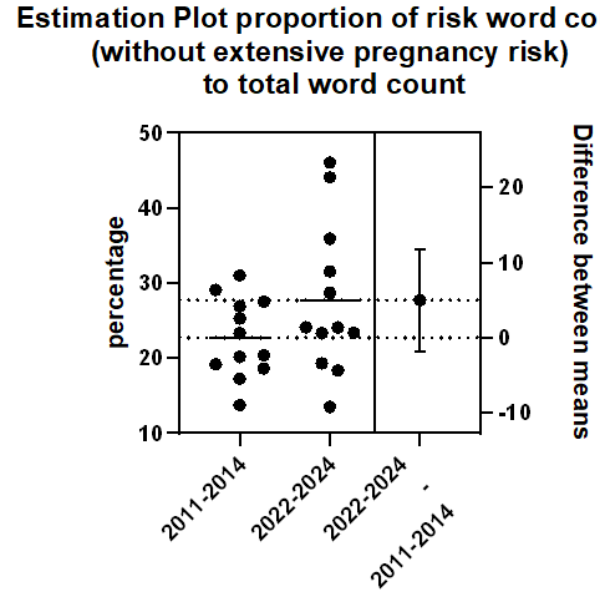

Figure 3.90: Proportion of total word count dedicated to the risk section (excluding extensive pregnancy-related content) in SIS/ICFs from 2011–2014 and 2022–2024 (t(22) = 1.522, p = 0.1422). The 2022–2024 SIS/ICFs allocated on average 27.7% of their total word count to risk information, compared to 22.7% in 2011–2014, a non-significant difference of 4.99% (± 3.28 SEM, 95% CI: –1.81 to 11.79).

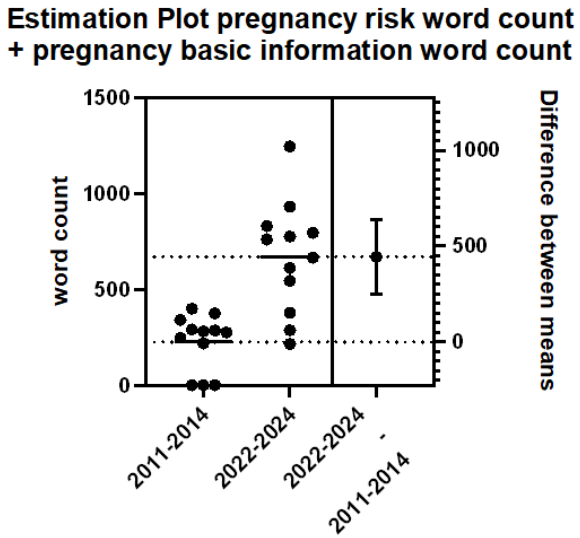

Figure 3.91: Comparison of the combined word count of pregnancy-related risks and general pregnancy information in SIS/ICFs from 2011–2014 and 2022–2024. SIS/ICFs released between 2022 and 2024 contained significantly more pregnancy-related information than those from 2011–2014 (t(22) = 4.756, p < 0.0001). The average combined word count for pregnancy risks and basic pregnancy information increased from 226.1 words (2011–2014) to 670.0 words (2022–2024), representing a highly significant mean difference of 443.9 words (± 93.3 SEM; 95% CI: 250.3 to 637.5). The effect size was large (η^2 = 0.507), indicating a substantial content expansion.

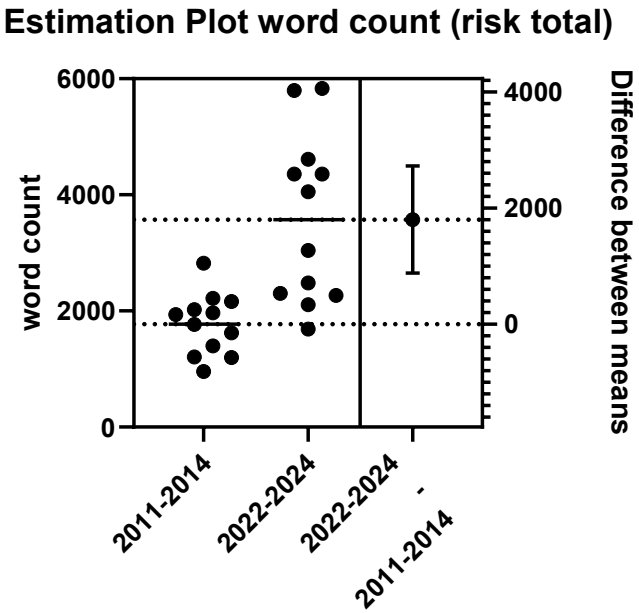

Figure 3.92: Comparison of total word count of the risk section (including pregnancy-related risks) in SIS/ICFs from 2011–2014 and 2022–2024 (t(22) = 4.049, p = 0.0005). The average word count in the newer documents was 3,574 compared to 1,773 in the earlier group, resulting in a mean difference of 1,802 words (± 445 SEM, 95% CI: 879 to 2,725).

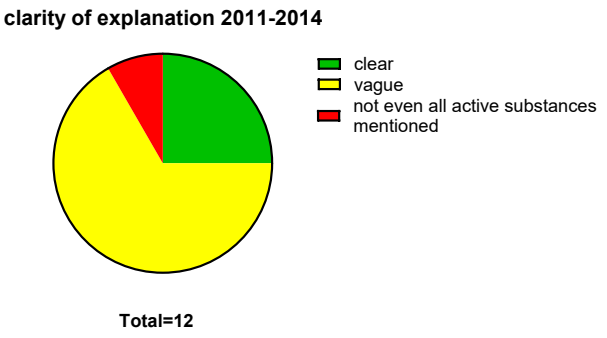

Figure 3.93: Clarity of explanation in the risk section of ICFs from 2011–2014. The pie chart illustrates how clearly the potential risks were described. The majority of ICFs (8 out of 12) provided vague descriptions, 3 gave clear explanations, while 1 did not even mention all active substances involved.

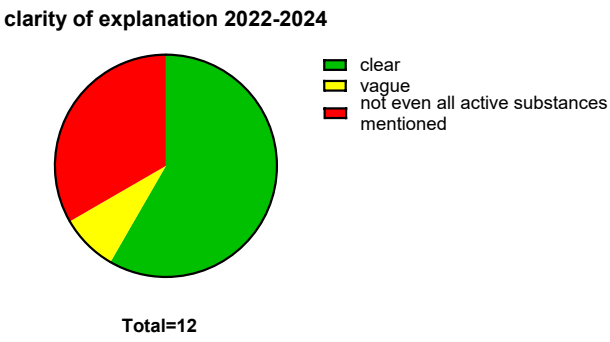

Figure 3.94: Clarity of explanation in the risk section of informed consent forms (ICFs) from 2022–2024. Compared to the earlier period, a greater number of ICFs (7 out of 12) provided clear explanations of risks. Vague descriptions were less frequent.

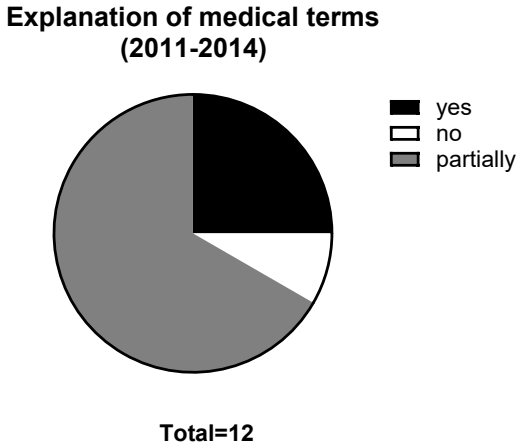

Figure 3.95: Explanation of medical terms in ICFs from 2011–2014. No ICF from this time period used visuals in the risk section.

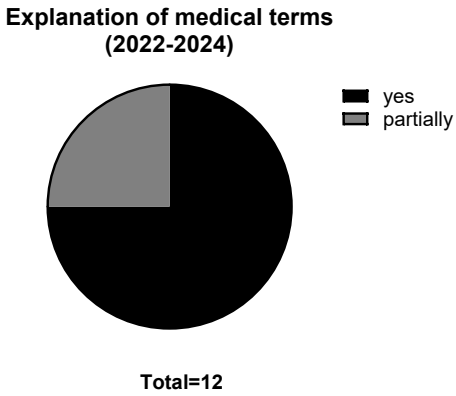

Figure 3.96: Explanation of medical terms in ICFs from 2022–2024. 75% of the documents provided “extensive explanations” (black), while 25% included partial explanations (gray). No cases without any explanation were observed in this period. Only one ICF from this time period used visuals in the risk section.

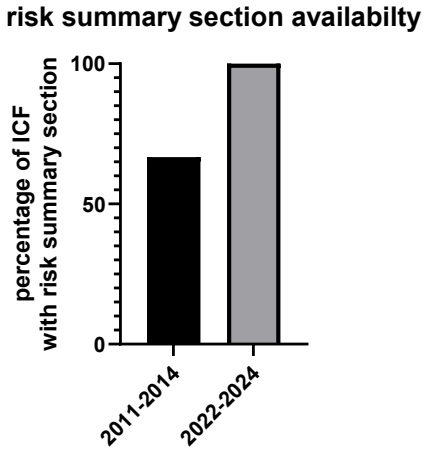

Figure 3.97: Availability of a dedicated risk summary section in ICFs. The proportion of informed consent forms (ICFs) that included a risk summary section increased from 2011–2014 to 2022–2024. While only around 67% of ICFs in the earlier period contained such a section, all ICFs from the later period included one.

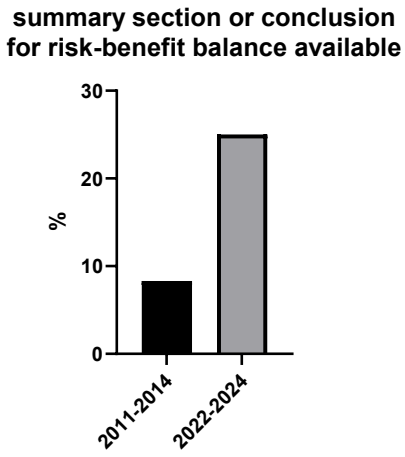

Figure 3.98: Availability of summary or concluding statements regarding risk-benefit balance. Only a minority of informed consent forms (ICFs) included a summary or conclusion addressing the overall risk-benefit balance. This feature was present in 8.3% of ICFs from 2011–2014 but increased to 25% in the 2022–2024 group. None of the ICFs from either group provided an elaborate discussion of the overall risk-benefit balance.

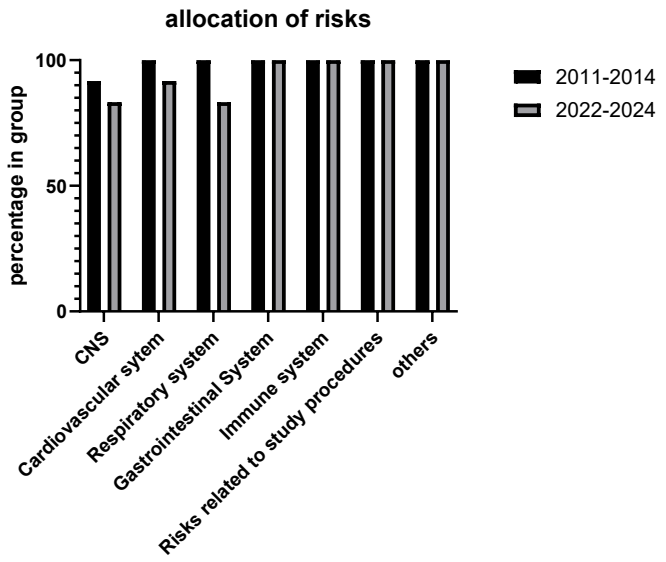

Figure 3.99: Allocation of risks in the risk section of ICFs from 2011–2014 and 2022–2024. Displayed are the proportions of informed consent forms (ICFs) in which risks were attributed to various systems or causes. Percentages refer to the proportion within each respective time group (n=12 per group).

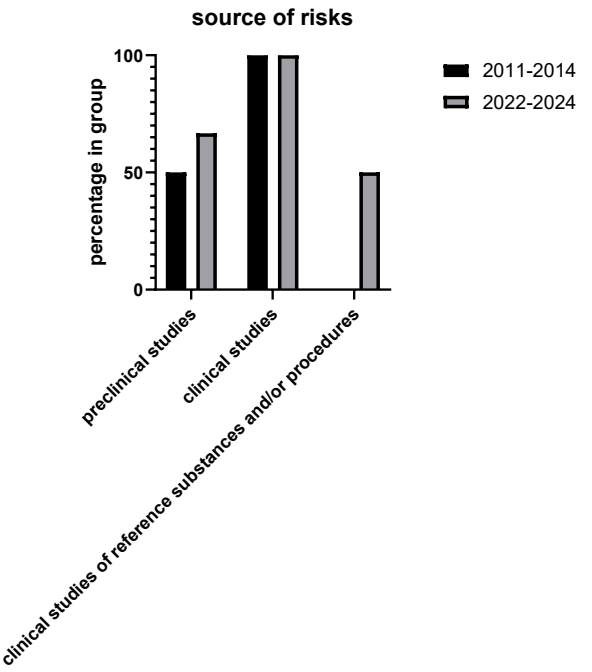

Figure 3.100: Stated sources of risks in the risk section of oncology ICFs from 2011–2014 and 2022–2024. The most commonly stated source in both timeframes was "clinical studies," followed by references to preclinical studies or prior studies involving reference substances and/or procedures. Each percentage is relative to the total number of ICFs in the respective group (n=12).

Risk-benefit comparison:

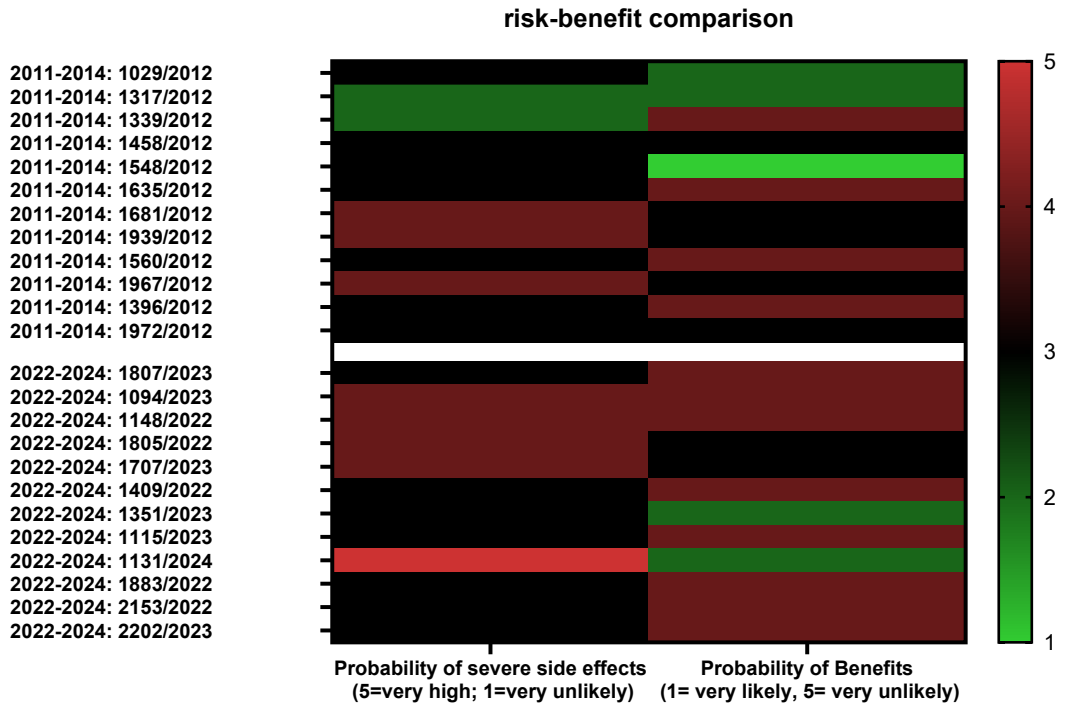

Figure 3.101: Heatmap of ICF-stated probability of severe side effects and probability of benefits across informed consent forms (ICFs) from both time periods. Each ICF was rated on a 5-point ordinal scale for both categories. Ratings were based on the language and presentation of risk and benefit in the patient information.

Benefit section data:

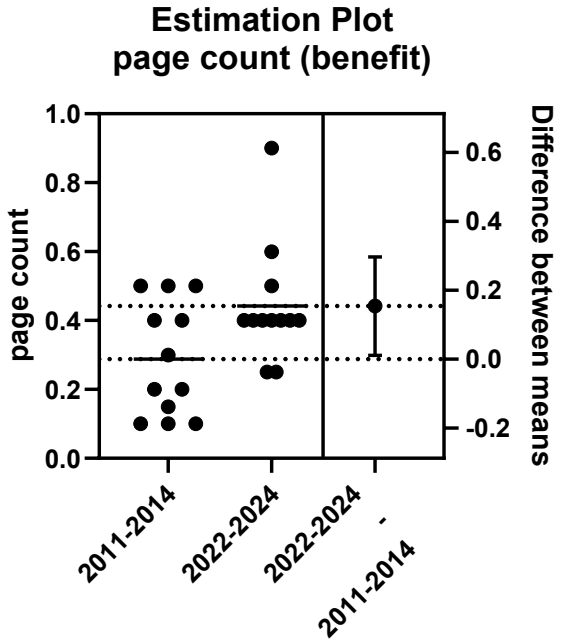

Figure 3.102: Estimation plot comparing the page count of the benefit section in ICFs between 2011–2014 and 2022–2024. A significant increase in benefit-related page count was observed in more recent ICFs (mean ± SEM: 0.29 ± 0.07 vs. 0.44 ± 0.07; p = 0.0355, unpaired t-test). The right panel displays the mean difference with 95% CI.

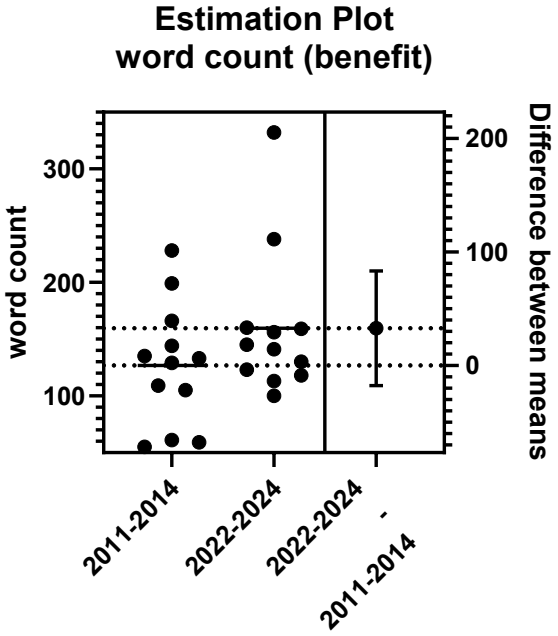

Figure 3.103: Estimation plot comparing the word count of the benefit section in ICFs between 2011–2014 and 2022–2024. Although a trend toward higher word count in the benefit section was observed for the newer group (mean ± SEM: 127 ± 10.3 vs. 160 ± 23.5), the difference did not reach statistical significance (p = 0.1937, unpaired t-test). The right panel shows the mean difference with 95% CI.

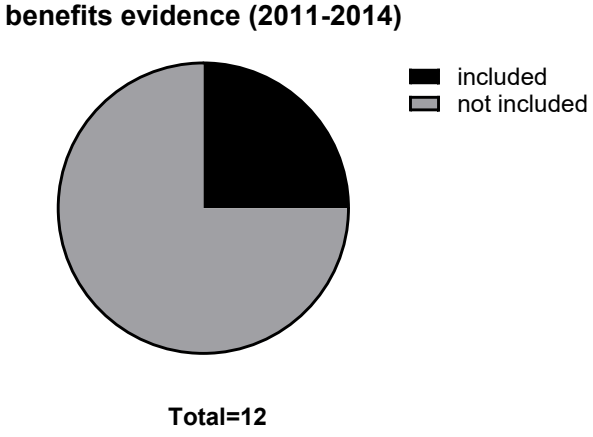

Figure 3.104: Evidence of described study benefits in ICFs of 2011-2014 period clinical trials (n = 12). Pie chart showing the degree to which the ICFs provided benefit-related evidence. The majority of ICFs provided no evidence (grey).

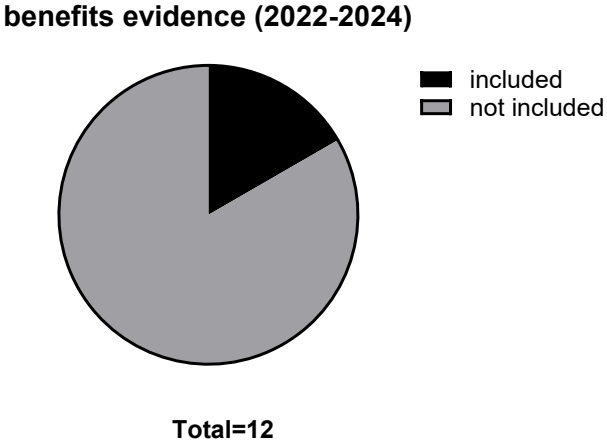

Figure 3.105: Evidence of described study benefits in ICFs of 2022-2024 period clinical trials (n = 12).

- All the ICFs of Experiment 2 included “statement on uncertainty of benefits”
- All but one ICF (period 2011-2024) from Experiment 2 included “explanation of indirect benefits”.

4. Discussion

4.1. Overview of Key Findings

The aim of this thesis was to analyze structural and content-related aspects of informed consent forms (ICFs), with a particular focus on risk communication and complementary domains such as data protection and biobanking. The analysis of 67 ICFs (of 56 different trials) from early- and late-phase clinical trials in 2 separate experiments revealed marked differences in document length and the extent of risk–benefit communication between trial phases and timeframes.

The following discussion interprets the findings of this thesis in the context of existing literature and regulatory frameworks. **Table 5** provides an overview of all tested hypotheses, their results, and statistical significance. The analysis revealed both expected and unexpected trends: while certain assumptions, such as the post-GDPR increase in ICF length and data protection content, were strongly supported, other hypotheses, like a consistent difference in overall word count between Phase 1/2 and Phase 3 trials, were not confirmed. These findings underscore both regulatory influences and structural factors as key drivers of ICF complexity and highlight the need to carefully differentiate between structural factors (e.g., internationality, trial design) and regulatory changes (e.g., GDPR) when evaluating ICF complexity and risk communication.

Table 5: Summary Of Hypotheses And Results

Hypothesis	Result	p-Value	Interpretation
Experiment 1			
Main Hypothesis H1: There is a significant difference in total word count and page count between SIS/ICFs for Phase 1/2 and Phase 3 clinical trials.	No significant difference in total word or page count between Phase 1/2 and Phase 3 ICFs	- Word: p = 0.441 - Pages: p = 0,524	ICF length is not strongly influenced by trial phase
H1a: SIS/ICFs for Phase 3 trials are longer (in word and page count) than those for Phase 1 trials.	Phase 3 ICFs are slightly longer but not significantly so	- Word: p = 0.441 - Pages: p = 0,524	Hypothesis not supported
H1b: Risk communication sections (in word count and page count) are more extensive in Phase 1 SIS/ICFs than in Phase 3 SIS/ICFs.	Risk sections are slightly longer in Phase 3, but not significantly	- Words: p = 0.691 - Pages: p = 0.35	Hypothesis not supported
H1c: The ICF-reported likelihood of severe adverse effects is higher in Phase 1/2 than in Phase 3 trials.	The probability of severe side effects is similar across phases	- p = 0.916	No difference in risk perception
H1d: The ICF-reported likelihood of benefits is higher in Phase 3 than in Phase 1/2 trials.	The probability of benefit is similar across phases	- p = 0.403	No significant difference in benefit perception
H1e: The overall number of countries involved in a clinical trial is positively associated with the word count and/or page count of the informed consent form.	Positive association between the number of countries and ICF length (Phase 1/2)	- Total words: p = 0.026 (Phase 1/2)	Significant for early-phase trials
H1f: Multinational trials are more likely to include standardized or visual display elements compared to trials with a smaller overall number of countries involved.	No significant link between the number of countries and visual elements	- Phase 1/2: p = 0.331; Phase 3: p = 0.771	Visual elements not associated with international scope

H1g: Phase 3 clinical trials are more likely to be multicentric, involving a higher number of countries, compared to Phase 1 trials.	Phase 3 trials involve significantly more countries	- $p < 0.0001$	Hypothesis supported
Experiment 2			
Main Hypothesis H2: SIS/ICFs released after the enforcement of the GDPR/ General Data Protection Regulation (2018) and after introduction of the CTR/ Clinical Trials Regulation are significantly longer and contain more extensive data protection information than those released before.	Post-GDPR ICFs are significantly longer and contain more data protection content	- Pages/Words: $p < 0.0001$ - Data protection words: $p = 0.0062$	Hypothesis supported
H2a: SIS/ICFs released after the GDPR are more likely to contain explicit references like "right to erasure" or data retention duration, than those released before.	Explicit GDPR-related references increased post-GDPR	- $p = 0.0458$	Significant increase in explicit data protection references
H2b: SIS/ICFs released after the GDPR are more likely to include separate, dedicated data protection and biobanking consent forms and/ or additional box selection.	More frequent use of separate consent/boxes for data protection & biobanking post-GDPR	- $p = 0.279$	Increase not statistically significant
H2c: Planned participant count is positively associated with the length of the risk communication section.	Participant count is not linked to the risk section	- $p = 0.522$ (2011–2014) - $p = 0.161$ (2022–2024)	No significant association
H2d: The presence of biobanking content is positively associated with total ICF word count.	ICFs with biobanking content are longer	- $p = 0.0378$	Hypothesis supported, but may reflect time period confounding
H2e: SIS/ICFs that include biobanking content are more likely to have a higher number of additional separate signature forms.	No significant link between biobanking content and the number of separate consent forms	- $p = 0.546$	Hypothesis not supported
H2f: The level of detail in biobanking sections (e.g., storage duration, reuse scope, sample coding, ...) correlates with the total word count of the ICF.	Biobanking complexity score positively correlates with ICF length	- 2011–2014: $p = 0.0051$ - 2022–2024: $p = 0.0408$	Hypothesis supported
H2g: The use of dedicated headings for biobanking content is associated with longer SIS/ICFs.	Dedicated biobanking headings not linked to longer ICFs	- 2011–2014: $p = 0.1939$ - 2022–2024: $p = 0.3507$	Hypothesis not supported
H2h: SIS/ICFs after 2018 have a significantly higher Biobanking word count.	Biobanking word count increased post-GDPR (absolute terms)	- $p = 0.0151$ (excluding forms) - $p = 0.1166$ (including forms)	Partial support, absolute increase

H2i: Biobanking consent forms have become more common and (when present) more extensive after 2018.	Biobanking consent forms are more extensive post-GDPR	- p > 0.19 (all comparisons)	No significant increase, but descriptive trend
H2j: SIS/ICFs, including flowcharts or visual elements, are shorter in word count.	ICFs with visual elements are significantly longer	- p = 0.0309	Visual elements linked to longer documents

4.2. Interpretation of Results

4.2.1. Experiment 1: Phase 1/2 vs. Phase 3 ICFs

ICF Length (H1, H1a, H1b)

- **Main Hypothesis H1: There is a significant difference in total word count and page count between SIS/ICFs for Phase 1/2 and Phase 3 clinical trials.**
- **H1a: SIS/ICFs for Phase 3 trials are longer (in word and page count) than those for Phase 1 trials.**
- **H1b: Risk communication sections (in word count and page count) are more extensive in Phase 1 SIS/ICFs than in Phase 3 SIS/ICFs.**

The analysis showed no statistically significant difference in the total word or page count of ICFs between early- and late-phase clinical trials (H1a). This finding is consistent with the data of Dukaew et al. (2023), who observed no significant differences in ICF length between early- and late-phase trials (average 22 pages, 7,915 words), suggesting that standardized templates may contribute more to document length than trial phase-specific tailoring. However, risk sections tended to be slightly longer in Phase 3 trials (H1b), though not significantly so. (47)

This may reflect the inclusion of more comprehensive safety data available in later development stages (also observable in Figure 3.20: Distribution of risk likelihood descriptions in Phase 1/2 ICFs. Risks were most commonly described using a combination of qualitative and quantitative elements (“mixture”), followed by purely qualitative and purely quantitative descriptions (n = 19)., and Figure 3.21). Nevertheless, both results suggest that structural standardization reduces variability across phases. The slight increase in the word count of Phase 3 trials might be due to enhanced trial complexity and the more common implementation of placebo- and standard treatment-arms in Phase 3 trials, requiring extensive explanation and ICF content.

Figure 3.24 shows that risk summary sections were also more common in Phase 3 trials, correlating with word count enhancement. Further potential confounding effects need to be acknowledged. The higher degree of multicentricity and internationalization in Phase 3 trials (H1g) could itself act as a structural driver of ICF length. Large-scale multinational studies often require additional details to comply with diverse regulatory frameworks and to address heterogeneous participant populations, which may inflate document size irrespective of trial phase. Taken together, these factors highlight that observed differences cannot be explained by the trial phase alone but are at least partially confounded by international scope and trial design complexity.

The absence of significant differences in ICF length or risk communication between early- and late-phase trials may reflect increasing harmonization of regulatory frameworks across Europe. Templates from ethics committees and guidance, such as EU Regulation No. 536/2014 and ICH-GCP, may have led to a convergence in the structural and content requirements of ICFs, overshadowing phase-specific variations. This suggests that the document structure is more influenced by regulatory compliance than by study design. (16,24)

In our Phase 3 sample, only about one-fifth of the ICFs provided a dedicated concluding statement that explicitly weighs potential benefits against risks. While risk summaries were somewhat more frequent in Phase 3 documents (≈70%), this does not equate to a transparent risk-benefit synthesis. This observation reinforces criticism from Kahrass et al. (2020) and Nusbaum et al. (2017), who argue that the lack of explicit benefit-risk framing may impair participants' ability to make well-informed decisions. (27,48)

Given that later-phase trials typically have more robust efficacy and safety data available, the underrepresentation of clear risk-benefit conclusions, especially in Phase 3 ICFs, seems like a missed opportunity to provide more decisive, participant-oriented information. (36)

Probability of severe side effects (H1c)

- **H1c: The ICF-reported likelihood of severe adverse effects is higher in Phase 1/2 than in Phase 3 trials.**

No meaningful differences were found for the ICF-reported probability of severe side effects (H1c), which indicates that risk framing is relatively uniform across phases, despite differences in actual risk profiles. This finding aligns with observations by Kahrass et al. (2020), who noted that risk descriptions are often vague and inconsistently quantified, which might explain the absence of phase-specific differences in our dataset. (27)

This also aligns with findings by Nusbaum et al. (2017), who emphasized that risk communication frequently uses ambiguous qualitative terms ('rare,' 'unlikely') rather than precise numerical estimates, which may contribute to uniform but vague risk perceptions. (48)

Coyle & Gillies (2020) further highlight that verbal descriptors alone can inflate perceived risks and reduce willingness to participate, while the combination of numerical and verbal descriptors improves accuracy and satisfaction. Paling (2003) adds that qualitative risk terms like 'low' or 'rare' are often interpreted inconsistently by patients and should be supplemented with clear numerical data or visual aids to "place risks into perspective". Beyond terminology, studies also show that how risk is framed (for example, as a potential loss versus a potential gain: 10% risk of death vs. 90% chance of survival) can significantly influence decision-making, sometimes more than the actual risk content itself. Although there is currently no consensus on a single "best" method to communicate risk, several guiding principles for effective and ethical risk presentation have emerged and are increasingly being adopted in clinical research contexts. (49–51)

Quick (2010) emphasizes that risk communication is inherently subjective and influenced by practitioners' values and experiences, which may explain the uniform, yet vague framing observed in our dataset. Daugherty et al. (1995) similarly highlight that early-phase oncology trials pose particular challenges for risk communication, as investigators often lack precise clinical data on adverse events, leading to qualitative and non-specific risk descriptions. (52,53)

Presenting risks in the same way across all trial phases can hide real differences in risk – especially in early phases, where side effects are less predictable. It is therefore important to tailor risk communication more closely to the specific uncertainties of each trial.

Probability of benefits (H1d)

- **H1d: The ICF-reported likelihood of benefits is higher in Phase 3 than in Phase 1/2 trials.**

Despite the typically higher efficacy expectations in Phase 3 trials, benefit communication remains similarly generic across phases. Kahrass et al. (2020) highlighted that benefit sections in ICFs often lack concrete evidence or quantitative benefit framing, which our findings confirm (see Figure 3.26: Evidence of described study benefits in ICFs of Phase 1/2 clinical trials (n = 19). Pie chart showing the degree to which the informed consent forms (ICFs) provided benefit-related evidence. The majority of ICFs provided no evidence (red), while minimal benefit evidence (yellow) and explicit benefit evidence (green) were rarely included. and Figure 3.27: Evidence of described study benefits in ICFs of Phase 3 clinical trials (n = 24). Pie chart displaying the frequency of benefit evidence in Phase 3 ICFs. Compared to Phase 1/2, a higher proportion of documents included minimal or explicit benefit-related statements, although many still lacked any substantiated benefit claims.). The most common phrasing identified by Kahrass et al. (2020) was vague statements such as "you may or may not benefit," which are also very common in german ICF and less than half of the documents (of all groups in both experiments) mentioned any form of supporting evidence for benefits. (27)

Trial Complexity and International Scope (H1e–H1g)

- **H1e: The overall number of countries involved in a clinical trial is positively associated with the word count and/or page count of the informed consent form.**
- **H1f: Multinational trials are more likely to include standardized or visual display elements compared to trials with a smaller overall number of countries involved.**
- **H1g: Phase 3 clinical trials are more likely to be multicentric, involving a higher number of countries, compared to Phase 1 trials.**

A key finding was the positive correlation between the number of participating countries and ICF length in Phase 1/2 trials (H1e), suggesting that multi-country studies require more complex information, such as multiple regulatory references or translations. While visual elements did not correlate with the overall number of countries involved (H1f), Phase 3 studies involved significantly more countries (H1g), which is consistent with their typical large-scale, multicenter nature.

H1e posited a positive association across phases. We observed it in Phase 1/2, but not in Phase 3 ($p = 0.212$), indicating phase dependence. The result shows a statistical trend that warrants further investigation. One possible explanation is that Phase 3 trials, as shown in Table 2: Study- and ICF-Level Characteristics (Experiment 1): Numeric Data (Mean ± SD) by study phase, involve a high level of international coordination and standardization, leading to a kind of „saturation effect". The informational and regulatory complexity may reach a saturation point, beyond which additional complexity through additional countries may no longer translate into further expansion of the ICF text. This may indicate a threshold effect in multinational trial communication structures. Such saturation could be driven by increasingly standardized documentation practices, as promoted in, e.g., EU templates. Standardization practices and regulatory harmonization in later-phase multinational trials may also contribute to this leveling-off effect. It is also possible that international complexity may have a larger influence on ICF length in earlier-phase trials, possibly due to greater variability in ethical or regulatory adaptation at earlier stages. Beyond this general explanation, several additional factors could account for the absence of a strong association in Phase 3 trials. First, global Phase 3 studies are typically coordinated by large sponsors or CROs/ Clinical Research Organizations who apply standardized templates across all regions, limiting variability not contingent on the number of involved countries. Centralized ethics submission procedures and, in some jurisdictions, formal caps on ICF length may further restrict expansion. Moreover, Phase 3 trials frequently involve therapies that are already

relatively well characterized, reducing the need for extensive explanatory text. Finally, not all additional countries add complexity equally; jurisdictions with harmonized regulatory standards may require minimal adjustments. (37–41,46)

In line with H1e, a positive association was found between the number of countries involved in a clinical trial and both the overall word count and the length of the risk communication section within the ICF. Notably, the correlation with the risk section was even stronger, suggesting that international complexity may particularly influence how potential risks are addressed in multilingual or multi-jurisdictional settings. These findings support an expanded interpretation of H1e, indicating that trial globalization affects not only the total length of ICFs, but also specific content areas such as risk communication.

While the data did not show a statistically significant association between the number of countries involved and the inclusion of visual or standardized display elements in ICFs (H1f), a phase-specific trend was observed: In Phase 1/2 trials, there was a slight, albeit nonsignificant, positive relationship between international scope and the number of display formats used, possibly due to cross-cultural adaptation needs. This pattern did not persist in Phase 3 trials, where the number of countries was generally high and variability was limited. Again, one possible explanation is a saturation effect/ ceiling effect: In later-phase trials, where international collaboration is already standard practice, the number of countries may no longer meaningfully differentiate trials in terms of visual adaptation. Conversely, in early-phase studies, where international participation varies more widely, sponsors may be more selective or responsive in adapting materials for diverse audiences. The lack of a significant correlation in either phase could also reflect that other factors, such as sponsor guidelines, local ethics committee expectations, or template-based authoring, have a stronger influence on visual content decisions. The overall higher number of display elements in Phase 3 trials may be driven not by the number of countries involved per se, but by other factors that correlate with later-phase trials, such as larger patient populations, broader inclusion criteria, or more advanced sponsor templates.

AT-DE Comparison:

Our results did not show a statistically significant difference in page or word count between Austrian and German ICFs, despite the slightly higher values for German documents. This contrasts with the findings reported in Reumann (2025), where a significant difference in page count ($p = 0.018$) was described for a smaller paired sample ($n = 7$). The Mixed Model (MM) analyses that led to this result were conducted by König and Eibensteiner in the context of the Europe-wide evaluation and reported in Reumann's thesis. (30)

The discrepancy may be attributed to both methodological and sample differences: In our study, the AT–DE comparison drew on a broader ICF pool, combining paired and unpaired documents of different phases, conditions that inflate within-group variance and reduce power for small effects. By contrast, Reumann's analysis focused on a narrowly defined paired Phase III cohort from 2023 CTIS submissions, modeled per trial, which yields tighter variance estimates and makes smaller effects detectable. This suggests that while German templates may encourage a more detailed structure, the variation in document length is not pronounced enough to be detected as significant in our dataset.

With regard to structural content, three additional aspects were examined: the presence of structured risk summary sections, the inclusion of a table of contents, and the placement of pregnancy/contraception-related information.

For the analysis of risk summary sections, we restricted the dataset to studies for which both an Austrian and a German ICF version were available. This allowed for a direct within-study comparison using paired data and a McNemar test. Although the German ICFs included structured risk summary sections more frequently (11 vs. 8), the difference did not reach statistical significance ($p = 0.083$). This approach, while methodologically stricter due to the use of paired comparisons, also resulted in a smaller sample size, potentially reducing the statistical power to detect a meaningful effect. Notably, the effect direction was consistent, and it remains plausible that a more lenient analytical approach or larger sample could have produced a significant result.

For the pregnancy/contraception section placement, we again used paired Austrian–German ICFs referring to the same clinical trials ($n = 11$) and applied McNemar's test. In 6 of the 11 pairs (54.5 %), the German ICF placed this information exclusively in the exclusion criteria section, while in none of the pairs was this exclusive to the Austrian ICF. This asymmetrical distribution was statistically significant ($p = 0.031$), indicating that German ICFs were more likely to use the exclusion criteria section for such information, whereas Austrian ICFs tended to place it in general "pregnancy/fertility" sections. This finding suggests a country-specific convention in content categorization, potentially reflecting template guidance or ethics committee preferences.

For the analysis of tables of contents, however, we did not limit the dataset to paired documents. Instead, all available Austrian and German ICFs were included to increase sample size and statistical power. Although paired comparisons would have been possible here as well, we opted for an unpaired comparison using the Mann–Whitney U test to capture the broader structural tendencies across countries. The result showed a statistically significant difference ($p = 0.0009$), with German ICFs including a table of contents far more frequently than Austrian ones. This suggests a systematic structural distinction between national templates.

The contrast between these approaches (two limited to matched pairs with a stricter test, one using a broader sample) highlights how methodological decisions influence the detection of structural differences. Both approaches offer value: the paired design provides internal control by eliminating study-level confounding, while the broader comparison enhances statistical power and generalizability. In summary, the choice of statistical test was guided not only by the structure of the data, but also by the potential impact on interpretation. For the dataset about the tables of contents, a stricter test would likely not have altered the interpretation, so we prioritized inclusivity of data over maximal methodological conservatism. This strategy aimed to balance robustness and sensitivity while maintaining transparency in the analysis of structural differences between Austrian and German ICFs.

Together, these results emphasize that despite regulatory harmonization through the CTR/CTIS, country-specific templates and ethics committee conventions continue to shape ICF structure. The choice of analytical strategy (paired vs. unpaired, strict vs. exploratory) plays a crucial role in uncovering such patterns and should be carefully aligned with the study objective. This pattern is consistent with Reumann (2025), who noted that German templates generally include more detailed, predefined subsections, particularly for data protection and risk information (Reumann, 2025, pp. 34–36). Both studies highlight that while regulatory harmonization (CTR/CTIS) has reduced variability, country-specific templates and ethics committee preferences still drive structural differences. (23,30)

4.2.2. Experiment 2: Pre- vs. Post-GDPR ICFs

Impact of GDPR on ICF Length and Content (H2, H2a, H2b)

- **Main Hypothesis H2: SIS/ICFs released after the enforcement of the GDPR/ General Data Protection Regulation (2018) and after introduction of the CTR/ Clinical Trials Regulation are significantly longer and contain more extensive data protection information than those released before.**
- **H2a: SIS/ICFs released after the GDPR are more likely to contain explicit references like "right to erasure" or data retention duration, than those released before.**
- **H2b: SIS/ICFs released after the GDPR are more likely to include separate, dedicated data protection and biobanking consent forms and/ or additional box selection.**

Our data confirms a strong increase in ICF length post-GDPR (H2), partly due to the expansion of data protection sections ($p < 0.0001$). Similar trends have been documented by Wisgalla et al. (2022) and Dukaew et al. (2023). Dukaew et al. link the increasing length of ICFs to stricter regulatory requirements, while Wisgalla et al. report that oncological ICFs commonly include around five pages dedicated solely to data protection, reflecting the growing emphasis on data privacy information and the contemporary expansion of „data protection clauses". Wisgalla also observes that ICF length has continuously increased over time. (47,54) This growth is also attributable to the expansion of data protection sections, which in our dataset added on average 643 words ($p = 0.0062$). However, when normalized to total ICF length, the relative proportion of data protection content remained stable (mean ≈ 13.7 % in both periods, $p = 0.9995$), indicating that while documents became longer, data protection content expanded in step with the overall text length rather than disproportionately. This indicates that the entire document is expanding rather than a single section, becoming disproportionately dominant. This trend aligns with findings in previous studies that point to a gradual 'inflation' of ICFs over time, which may challenge participants' ability to identify the most critical information. (54)

The analysis for H2a was based on a predefined set of representative data protection references commonly expected in ICFs (e.g., GDPR, data retention, right to erasure, ...). It does not account for every possible phrasing or reference related to data protection. For H2a, the explicit references to GDPR-related rights significantly increased ($p = 0.0458$), confirming a shift towards more precise legal terminology.

For H2b, due to the small number of cases per individual variable, we conducted a combined analysis of two related indicators: additional consent elements for data protection and for biobanking. Both reflect an effort to obtain more specific and modular consent. Analyzing them jointly allowed for a more statistically meaningful comparison while preserving conceptual clarity.

While GDPR implementation has led to more comprehensive data protection statements, this often increases textual complexity and risks overwhelming participants with technical legal terminology. (55–59)

Similarly, the risk sections also grew in absolute length (page count $p = 0.0005$; word count $p = 0.0023$/ Figure 10.15 and Figure 3.89), but the relative share of these sections within the ICFs did not significantly change. This suggests that the increase in ICF size post-GDPR may be a global inflation of all sections rather than a selective extension of individual parts. The proportional data reinforces that GDPR compliance may have added content across the entire document rather than shifting the internal balance between sections.

Taken together, these findings indicate a broader, more standardized approach to data protection, without fundamentally changing the proportion of the ICFs dedicated to these topics.

Participant Count and Cumulative Risk Exposure (H2c)

- **H2c: Planned participant count is positively associated with the length of the risk communication section.**

Interestingly, participant count showed no association with the length of risk sections (H2c), indicating that document complexity may be more a result of regulation than of study size. However, this finding does not account for the ethical implications of scaling risk exposure across larger populations. While each participant may be exposed to a similar individual risk, the cumulative ethical burden increases when a risk (however small on an individual level) affects thousands of participants.

To address this perspective, we propose an exploratory metric termed Cumulative Risk Exposure (KRE), an idea originally developed by Eva Maria Zebedin-Brandl. KRE is defined as:

$$\mathbf{KRE = \sum (N \times P_i \times S_i \times D_i \times W_i)}$$

- N ... number of participants
- P_i ... probability of risk i
- S_i ... severity of risk i
- D_i ... duration of risk i
- W_i ... optional ethical weighting factor for irreversible outcomes or significant quality-of-life impacts.

In practice, different types of risks (e.g., acute vs. long-term) could be evaluated separately, resulting in individual KRE values (KRE_1, KRE_2, ...), which may then be aggregated (e.g., $KRE_{total} = KRE_1 + KRE_2$). This structure allows for distinguishing between frequently occurring but less severe events and rarer but more serious long-term risks.

The KRE concept aims to highlight that a risk considered acceptable for one individual might no longer be ethically acceptable when aggregated across a large cohort, especially if the anticipated benefit remains uncertain or unevenly distributed. KRE could serve as a complementary, **quantitative lens on cumulative risk** to address the **ethical scaling of risk** in modern clinical trials.

Biobanking and Additional Consent Elements (H2d–H2i):

- **H2d: The presence of biobanking content is positively associated with total ICF word count.**
- **H2e: SIS/ICFs that include biobanking content are more likely to have a higher number of additional separate signature forms.**
- **H2f: The level of detail in biobanking sections (e.g., storage duration, reuse scope, sample coding, ...) correlates with the total word count of the ICF.**
- **H2g: The use of dedicated headings for biobanking content is associated with longer SIS/ICFs.**
- **H2h: SIS/ICFs after 2018 have a significantly higher Biobanking word count.**
- **H2i: Biobanking consent forms have become more common and (when present) more extensive after 2018.**

Biobanking content increased in both frequency and word count after GDPR (H2f, H2h, H2i), with a partial but not statistically significant rise in the use of separate consent forms or checkboxes. The presence of biobanking information correlated positively with ICF length (H2d). However, no strong link was found between the inclusion of separate biobanking headings and total ICF length (H2g).

The biobanking complexity score and the mere presence of biobanking content showed a significant correlation with ICF length in both periods (H2f, H2d), suggesting that the level of detail adds to document size. While ICFs, including biobanking content, tended to be longer, this effect may reflect overall study complexity rather than the biobanking component per se. This comparison of H2d should be interpreted as exploratory due to the small number of ICFs without biobanking content (n=3) and potential confounding by time period. Although ICFs including biobanking content showed a significantly higher total word count compared to those without ($p = 0.0378$), it should be noted that two of the three ICFs without biobanking content originated from the earlier time period (2011–2014), which was generally associated with shorter ICFs overall. Thus, this difference might at least partially reflect temporal changes rather than biobanking content alone.

The observed increase in biobanking content reflects not only regulatory shifts but also the growing role of molecular and genetic analyses in clinical research. Detailed information on sample storage, secondary use, and data linkage is becoming essential for regulatory compliance and participant autonomy. At the same time, evidence suggests that critical genomic aspects remain frequently underreported: Dukaew et al. (2023) found that information on the involvement of whole-genome sequencing was missing in more than half of industry-sponsored ICFs (54.7%), alongside other highly related key aspects such as experimental procedures and commercial profit sharing. This contrast highlights a central challenge: while ICFs expand in length and detail, they may still fail to provide participants with the most relevant information for truly informed decision-making. The evolution of genomic and biomarker-driven research underscores the need for concise yet comprehensive communication strategies that can balance transparency with readability. The observed growth in biobanking content may align with evolving governance expectations. (47,60)

Biobanks are defined as “structured resources with established governance mechanisms that ensure transparent communication about the acquisition, storage, and use of samples, as well as the protection of donor rights and stakeholder interests” (Annaratone et al., 2021). This emphasis on clear governance aligns with best practices in modern biobank design, which aim to balance scientific utility with ethical responsibility and public trust. (60)

Visual Elements as Indicators of Document Complexity (H2j):

- **H2j: SIS/ICFs, including flowcharts or visual elements, are shorter in word count.**

Visual elements like flow charts were associated with longer ICFs (H2j), likely because graphics are more frequently used in larger, sponsor-driven templates. Therefore, visual elements may be a marker of overall comprehensiveness rather than simplification.

This may indicate that visualizations are currently being used as supplements rather than replacements for textual explanations. While visuals can improve comprehension, their current integration does not seem to reduce textual burden. Future approaches could investigate whether visual summaries can effectively condense repetitive or overly detailed text without compromising regulatory requirements.

Although visual elements were associated with longer ICFs, their potential to enhance participant understanding should not be overlooked. Empirical studies in health communication show that visual risk communication tools, such as icon arrays, paling scales, or pictorial scales, can reduce subjective information overload and improve participants’ ability to recall or contextualize risk-related information (51,61,62)

William J. Heerman et al. emphasize that visual aids enhance comprehension for individuals of all literacy levels, while Bancilhon et al. (2023) demonstrate that icon arrays improve accuracy and lower cognitive load compared to text-only formats. Additionally, Gisladottir et al. (2022) showed that patient-facing visual consent tools and personalized risk visualizations were preferred over text-only formats and supported shared decision-making. (63–65)

Coyle & Gillies (2020) note that visual aids such as pictographs and bar charts can help improve the understanding of probabilistic information and reduce framing biases, yet these methods are still underutilized in clinical trial ICFs. Several studies summarized in the review by Coyle and Gillies (2020) indicate that the presentation format of probabilistic information has a substantial impact on participants' understanding and decision-making. For instance, participants exposed to verbal descriptors alone were not only less likely to participate in clinical trials but also significantly overestimated the likelihood of adverse events compared to those receiving combined verbal and numerical formats. Moreover, many individuals demonstrated substantial difficulties interpreting verbal risk labels or basic probability figures correctly. These findings underscore the limitations of purely textual or vague probability information and highlight the potential benefits of supplementing informed consent materials with numerical data, preferably in frequency formats. (66)

This also aligns with Seiling et al. (2024), who highlight Article 12(7) of the GDPR (also described in recital 60) (18), which explicitly encourages the use of **standardized privacy icons** to provide an “easily visible, intelligible and clearly legible” overview of data processing. Incorporating such visual elements in ICFs could similarly improve navigation and comprehension. (18,67)

This reasoning is further supported by theoretical frameworks such as Cognitive Load Theory and the Cognitive Theory of Multimedia Learning, which build on Dual-Coding Theory. Sweller (1988) emphasizes that extraneous cognitive load (such as overlong text) hinders processing in working memory, while Mayer (2005) shows that presenting information via both verbal and visual channels enables meaningful learning by constructing linked verbal and pictorial mental models. A detailed overview of these concepts can be viewed in Table 6: Theoretical Foundations of Multimedia-Based IC-/Risk-Communication (55,57–59)

Future research should test whether visual summaries could replace redundant text, rather than merely complementing it, thereby streamlining consent information without sacrificing completeness. As outlined in Article 12 of the GDPR, information must be provided in a concise, transparent, and easily accessible form. This supports the use of visual aids, modular structures, and clear navigation markers, which can enhance comprehension and guide participants through complex consent documents. (18)

Descriptive Insights from Experiment 2 (Non-Hypothesis-Driven Data)

The descriptive results of Experiment 2 highlight a clear shift in the visual presentation of ICFs over time. While only 16.7% of pre-GDPR ICFs included tables, every ICF from 2022–2024 contained tabular elements, suggesting that modern templates increasingly incorporate structured data summaries. This trend is mirrored by a moderate increase in the use of flowcharts (16.7% to 25%) and the introduction of visual elements such as cartoons (16.7%), which were absent in earlier documents. These observations may indicate a growing recognition of the value of visual communication, even if our analyses for H2j suggest that visuals are currently more a marker of document comprehensiveness than a true simplification tool.

Regarding study design, there is a noticeable increase in trials including a standard treatment arm (58.3% to 83.3%) and a simultaneous decline in placebo-controlled designs (50% to 25%). This may reflect ongoing ethical debates around the use of placebos, especially in oncology, and a shift towards comparative effectiveness studies. While these factors were not part of our core hypotheses, they provide context for the evolving structure and informational content of ICFs, which must adapt to more complex trial designs.

Overall, these descriptive findings underscore a broader trend towards increased formal refinement, more structured visual presentation, and greater linguistic precision in Austrian ICFs in recent years. Future research should examine whether these visual enhancements genuinely improve comprehension or simply contribute to increased document length. While it remains uncertain whether such changes truly help participants understand the information, they indicate a move from simply listing information to presenting it in a way that more clearly supports the step-by-step evaluation of participation.

4.2.3. Cross-Experiment Insights and Comparison with Literature:

Our results confirm general trends reported in the literature: ICFs are too long and often fail to enhance comprehension (Dukaew et al., 2023; Nusbaum et al., 2017). Dukaew et al. (2023) showed that industry-sponsored ICFs, averaging 22 ± 7 pages, devote more than half of their length to trial procedures, risk descriptions, and confidentiality provisions, while still lacking essential elements such as a clear explanation of experimental aspects or commercial implications. Nathe & Krakow (2019) found that oncology consent forms have increased nearly tenfold in length since the late 1980s, with comprehension inversely correlated to page count. Bolcato et al. (2024) similarly warn that excessive bureaucratization of the consent process, particularly through lengthy documents, can generate distrust among patients and practitioners, leading to a **paradoxical reduction** in informed decision-making. (26,47,48,68)

The dominance of legal and procedural information (especially post-GDPR) mirrors findings by Wisgalla (2022), who observed an increase in legalistic data protection text at the expense of plain-language explanations. Moreover, our results align with Kahrass et al. (2020), who showed that early-phase oncology ICFs rarely provide precise benefit information, while risk sections often rely on non-quantitative descriptors. (27,54)

4.3. Limitations

This study is limited by its focus on German-language ICFs from Austria and Germany, which limits transferability to other regulatory settings and may not represent global practices. Future research could benefit from a cross-linguistic comparison to evaluate whether these trends hold in non-German contexts.

The analysis was limited to document text and structure; participant comprehension was not tested, so conclusions on understandability remain indirect.

In addition to our inclusion criteria, the ICFs stem from specific registries and sponsor submissions, which may introduce selection bias towards standardized templates. In Experiment 1, a considerable number of potentially eligible ICFs could not be included in the analysis because their format prevented reliable processing in Microsoft Word (e.g., scanned PDFs or image-based documents). Anecdotally, these excluded ICFs appeared to contain a disproportionately high number of cartoons or other visual elements. Their omission may have introduced bias by underrepresenting visually enriched formats in the dataset, potentially

affecting conclusions about the prevalence and impact of such features. This limitation did not apply to Experiment 2, where all identified ICFs could be processed and included in the analysis.

Our study did not assess participants' literacy or educational background, which Taylor (1999) identifies as key factors influencing comprehension of informed consent materials. Additionally, timing and opportunities for discussion, highlighted as critical by Taylor, were outside the scope of our document-based analysis. (3)

A further limitation of this study is that all coding and data extraction were performed by a single researcher. While predefined coding matrices and cross-validation steps were applied to ensure consistency, the absence of multiple coders or formal inter-rater reliability testing may introduce potential bias in content categorization. Future studies should consider employing dual coding or independent validation to enhance the robustness of findings. Interrater reliability measures (e.g., Cohen's kappa or Krippendorff's alpha) can be used to quantify coding consistency and mitigate individual bias. (30)

4.4. Practical Implications and Future Directions

The findings suggest that regulatory changes (e.g., GDPR) drive much of the complexity and length of ICFs. A key challenge for future practice is balancing compliance with readability. Efforts such as modular templates, plain language standards, and the integration of visual aids should be explored to enhance patient understanding. Future studies should combine document analysis with empirical assessments of patient comprehension, possibly testing alternative formats (e.g., layered information or interactive digital consent) and evaluating the real-world effectiveness of current ICF practices. In this context, emerging digital and AI-assisted consent platforms could offer tailored presentations of study information, adapting content to participants' literacy levels and information needs while ensuring that all regulatory requirements are met. (28,32)

Our observations are supported by evidence from Koonrungsesomboon et al. (2016), who demonstrated that the SIDCER-informed consent template significantly increased participants' understanding compared to conventional ICFs (60.8 % vs. 41.4 %, $p = 0.002$), while being shorter and more focused, with no difference in reading time (30 vs 30 minutes, $p = 0.959$). The SIDCER informed-consent template (Strategic Initiative for Developing Capacity in Ethical Review) assembles all mandatory ICF elements from ICH-GCP, 45 CFR 46, and the Declaration of Helsinki in a concise, easy-to-read format using boxes, colors, and illustrations, with color-coded placeholders for study-specific text and visuals. These findings reinforce our conclusion that reducing length and improving structure (potentially through visual aids) can enhance comprehension without compromising content. (40,69)

Malik & Mejia (2014), citing recommendations from the National Cancer Institute (NCI), suggest that main consent documents should not exceed 6–9 pages, with supplemental materials (e.g., appendices or handbooks) providing additional details. This layered approach aligns with other proposals for modular ICF designs that separate core information from secondary content to improve readability and focus. (70)

Nusbaum et al. (2017) further highlight that informed consent training is often insufficient, particularly regarding risk communication, which suggests that improving staff communication skills is as important as refining document structure and content. (48) Future approaches could also harness modern communication technologies, such as digital platforms, multimedia tools,

or AI-assisted consent systems, to complement personal interaction and support participants in navigating complex information.

When adopting digital/e-consent, sponsors should document: 1. accessibility/usability testing, 2. data-protection and eIC version-control measures, 3. procedures for providing participants with a copy, and 4. a plan to evaluate comprehension outcomes- all elements explicitly anticipated by existing FDA/OHRP guidance. (35)

4.5. Concluding Remarks

In summary, while ICF length and structure are influenced by trial phase and international scope, a more profound impact arises from regulatory developments such as GDPR. While Experiment 1 did not isolate GDPR effects, its country/template contrasts were modest relative to the clear post-GDPR expansions observed in Experiment 2; the combined pattern points to regulatory language as the larger driver. Risk communication remains a critical but under-optimized component, often overshadowed by legal content. The results underline the need for clearer, more concise, and patient-centered ICFs, with standardized approaches to risk–benefit framing and biobanking information that are effectively adaptable to different kinds of study designs. This suggests that future efforts to simplify ICFs should focus on regulatory language and legal requirements rather than trial design alone. The practical target is how ICFs are written for a given design, not changing the design itself: Simplification should focus on harmonizing the legally required wording and its presentation, for example, via modular "master-ICF" templates (a standardized core with study-specific modules), adaptable to complex modern designs such as platform, umbrella, and basket trials.

Beyond structural and regulatory considerations, the ethical principle of respect for autonomy demands that participants can meaningfully understand the provided information. The growing complexity of ICFs, particularly due to legalistic GDPR clauses, raises concerns about whether participant comprehension is genuinely improved or hindered. This gap between regulatory compliance and participant empowerment remains a critical challenge.

Millum and Bromwich (2018) argue that valid consent depends less on exhaustive detail and more on ensuring a shared understanding of what is being agreed to. This aligns with our findings that post-GDPR ICF expansions may increase length without necessarily improving comprehension. Instead, clear communication and focus on essential risk-benefit information appear critical for facilitating meaningful consent. (5)

Our findings echo concerns expressed in the Belmont Report (1979), which highlights that informed consent must balance the quantity of information with the participant's capacity to comprehend it. The Report emphasizes that „the manner and context in which information is conveyed is as important as the information itself ". The increasing length and complexity of ICFs (partly driven by regulatory requirements) may therefore challenge the Report´s ethical principle of "respect for persons", as comprehension can be compromised despite, or even because of, formal compliance. Dilatory, obstructive, or otherwise misleading ICF design must be avoided, as such practices risk rendering consent not only legally invalid but also ethically untenable.

Genuine informed consent is not a mere matter of formal compliance with regulation, but a moral precondition for justice, dignity, and the recognition of participants as autonomous persons. History has shown that law without ethics can degenerate into coercion and abuse; therefore, ethical responsibility and legal safeguards must work in concert to ensure that informed consent serves its true purpose: the protection of human dignity and the possibility of

just participation in research. To this end, consent templates should be designed to minimize the inclusion of counterproductive elements, as a precondition for the possibility of genuine informed consent. Ultimately, the goal should be to achieve a fair distribution of the capability to be adequately informed across diverse types of human individuals, ensuring that informed consent is accessible not only in principle but also in practice. (11–15)

4.5.1. Structural and Legal Drivers of Ineffective Consent Practices:

While the shortcomings of current SIS/ICFs, particularly their excessive length, complexity, and limited comprehensibility, are well documented, the structural causes underlying these design issues warrant further discussion about potential reasons for the persistence of complex and ineffective SIS/ICFs.

Nathe and Krakow (2019) suggest that the dramatic increase in ICF length in industrialized countries (nearly tenfold from 1987 to 2010) may be driven, at least in part, by fear of litigation and overregulation. The authors hypothesize that regulatory bodies and legal departments often demand inclusion of exhaustive risk disclosures and legally precise language, which inadvertently hampers patient understanding rather than enhancing it (p. 6). (68)

Furthermore, the institutional inertia within ethics review boards (IRBs) and the heterogeneous demands across trial sites may contribute to bloated consent documents. For example, standardized templates provided by cooperative groups are frequently expanded by local IRBs, increasing average page counts from 13 to 17 (Nathe & Krakow, 2019, p. 6-7). This “redundancy”, especially in sections dealing with data protection, financial compensation, and confidentiality, often overwhelms patients and distracts from the truly critical trial-specific information. (68)

These findings underscore the tension between legal safeguarding and ethical clarity. While comprehensive disclosure is legally motivated, it may paradoxically obscure rather than clarify key elements of a trial, thereby undermining the very autonomy it seeks to protect. Addressing these issues likely requires systemic changes, including streamlined regulatory frameworks, harmonized IRB policies, and a shift in emphasis from “legal completeness” to “communicative effectiveness”.

4.5.2. Communicating Clinically Relevant Endpoints in ICFs:

Confirmatory studies are expected to use clinically relevant endpoints that reflect disease burden (or valid surrogates) and support benefit–risk assessment for licensing. E8(R1) further emphasizes that endpoints should be well-defined, measurable, and meaningful to patients, with patient input helping to select what matters (e.g., symptoms, functioning, PROs) and to explain how and when endpoints are ascertained. Translating these design requirements into the ICF means that participant-facing summaries should state clearly what “success” is, why it matters to patients, when it is measured, and what the endpoint can/cannot tell them. (36)

In practice, an ICF “endpoint summary” can be expressed in few sentences that 1. name the primary endpoint in plain language, 2. explain patient relevance (e.g., survival, symptom relief, daily functioning), 3. specify assessment timing (visits/windows), and 4. if a surrogate is used, briefly state its value and limitations. Where appropriate, include one line that conveys the intended treatment effect in simple estimand terms (e.g., “comparing time to progression between groups”). This aligns consent content with E8(R1)’s quality-by-design focus on endpoints that are clinically meaningful and relevant to patients. (36)

4.5.3. Limits of Comprehension: Structural and Sociocultural Barriers

Despite receiving and signing detailed informed consent documents, many participants in oncology trials do not fully understand the nature, purpose, or implications of the research they are enrolled in. Nathe and Krakow (2019) highlight two interrelated factors that contribute to this phenomenon: insufficient content quality and deeply rooted sociocultural misconceptions about medical research. (68)

On the structural level, the authors note that essential elements such as the experimental nature of the trial, the distinction between treatment and research, and the lack of guaranteed personal benefit are frequently underrepresented or omitted in consent forms. This is consistent with recent findings from Dukaew et al. (2023), who reported that in two-thirds of industry-sponsored ICFs (67.2%), the experimental aspects of the research were insufficiently addressed. Such omissions are particularly problematic, as they may reinforce misconceptions by blurring the distinction between clinical care and experimental intervention. In one study referenced by Nathe and Krakow, only 46% of participants recognized that the primary purpose of the trial was to benefit future patients, not themselves (p. 5). This underlines a systemic failure to communicate equipoise and research ethics transparently. (47,68)

At the same time, sociocultural factors further complicate comprehension. Many patients enter the consent process with a strong belief in the therapeutic intent of the study, a phenomenon commonly referred to as the “therapeutic misconception” (Henderson et al., 2007; Nathe & Krakow, 2019). Common misunderstandings about modern treatments, such as the belief that “targeted therapies” or “immunotherapies” are inherently less toxic, also skew risk perception and decision-making (Nathe Krakow, p. 4–5). Such assumptions persist even when forms are made more readable, indicating that simplified language alone cannot resolve deeper misconceptions about clinical research. (68,71)

Wisgalla & Hasford (2022) confirm this problem in their analysis of informed consent (IC) practices, noting that the **therapeutic misconception** (the failure to recognize the distinction between clinical care and research) is both widespread and directly linked to invalid consent. Their review cites meta-analytic data showing that 37.6 % of participants exhibited this misconception, with 30 % of oncology trial participants assuming the experimental treatment was already proven most effective. They also highlight that only 64.1 % of participants knew alternative therapies would be available if they withdrew from the study, underscoring how misunderstandings can affect voluntariness. Such beliefs can be reinforced when IC materials fail to communicate the uncertainty of personal benefit, neglect to specify alternative treatment options, or present benefits vaguely compared to extensive descriptions of risks. (54,72,73)

Both Nathe & Krakow (2019) and Wisgalla & Hasford (2022) converge on the point that overcoming therapeutic misconception requires more than linguistic simplification. Wisgalla & Hasford propose a shift from legalistic, liability-driven IC practices toward autonomy-driven consent, treating IC as a process rather than a form. They advocate combining readable IC materials with substantive, iterative conversation between participants and the research team, engaging patients and patient experts in co-developing materials, and addressing misconceptions directly during the consent process. Together, these insights point to the need for consent processes that go beyond linguistic simplification and address patients’ expectations, beliefs, and biases directly, possibly through person-centered communication, visual aids, and iterative clarification during the trial process. (54,68)

4.5.4. Theoretical Background: Learning and Cognition in Multimedia Contexts

Cognitive Theories Supporting the Use of Visual Aids in Risk Communication

The use of visual aids in risk communication and informed consent materials can be theoretically grounded in established cognitive theories of learning. The following table summarizes three relevant frameworks and their implications for the design of SIS/ICFs.

Table 6: Theoretical Foundations of Multimedia-Based IC-/Risk-Communication

Theory	Principle	Application in SIS/ICFs and risk communication
Dual-Coding Theory (74)	According to Paivio's Dual Coding Theory, memory performance can be enhanced by presenting information through both verbal and visual channels. Each channel forms its own modality-specific trace (logogens for verbal input, imagens for visual), which allows for both automatic and referential encoding. This mnemonic system and its dual representation improve recognition and recall because verbal and nonverbal systems can be activated independently or in tandem (Paivio, 1986, pp. 75–76). In risk communication and informed consent, the combined use of text and imagery increases the likelihood that key concepts will be retained and understood.	Use corresponding images alongside written explanations in consent forms to support dual encoding. This helps recipients encode information through both channels, improving comprehension and recall of key risks.
Cognitive Load Theory (55,56)	The Cognitive Load Theory, as outlined by Sweller et al., distinguishes between three types of **cognitive load**: **intrinsic** (content complexity), **extraneous** (presentation-induced), and **germane** (learning-relevant). Effective communication design (such as in SIS or ICFs) should aim to reduce extraneous load, manage intrinsic complexity through sequencing or scaffolding, and encourage germane load via engagement strategies. Working memory is limited, and extraneous load hinders learning.	Reduce unnecessary and redundant information in SIS/ICFs to prevent overload. Present only core risk information clearly and concisely. Structure consent forms to avoid split attention (e.g., using either narration or text, not both), highlight key concepts, and eliminate distractions to support efficient processing.
Cognitive Theory of Multimedia Learning (57–59)	Learning improves when learners actively process coordinated verbal and visual input. Mayer's Cognitive Theory of Multimedia Learning (CTML) builds on dual coding and cognitive load theory and posits that people learn more deeply from words and pictures together than from words alone. The theory identifies three core cognitive processes: selecting, organizing, and integrating verbal and visual information. Effective multimedia instruction should support these processes while minimizing unnecessary mental effort. - CTML is operationalized through empirically validated design principles: o Multimedia Principle: Present words and relevant images together. o Contiguity Principle: Place corresponding text and images close in space and time. o Split-Attention Principle: Avoid simultaneous visual sources (e.g., text and image) that compete for attention. o Modality Principle: Use audio narration instead of on-screen text with graphics to avoid visual overload. o Coherence Principle: Eliminate extraneous content to focus learners' limited cognitive resources on essential material. Together, these principles help learners build coherent mental models and improve comprehension.	Structure informed consent materials to align with CTML principles. Present critical information using complementary visuals and spoken or written explanations (Multimedia Principle). Align text and images spatially and temporally (Contiguity), avoid overwhelming the visual channel by narrating visuals rather than overlaying text (Modality, Split-Attention), and remove distracting or nonessential content (Coherence). This supports efficient processing, comprehension of key risks, and retention of essential concepts.

4.5.5. Evolving Informed Consent: From Multimedia Tools to AI-Based Solutions

Looking ahead, emerging technologies, particularly AI-powered tools, could play a vital role in overcoming the limitations of current informed consent practices. Interactive digital systems, such as conversational agents or adaptive multimedia platforms, offer the potential to tailor explanations dynamically to a patient's background knowledge, language level, and emotional state and to respond empathetically to patients' concerns and to detect therapeutic misconceptions. For example, natural language processing (NLP) models could identify and clarify misunderstood concepts in real time, while dynamic and reactive visualizations or explainer videos generated by AI could reinforce understanding of complex trial designs or probabilistic outcomes.

Naturally, the implementation of such novel and unexplored technologies is not without unknown risks. Their use must be approached with caution, and it should be emphasized that healthcare professionals remain ultimately responsible for ensuring ethical standards and genuine patient understanding. The integration of AI into the consent process must therefore be carefully supervised, transparent, and ethically sound with ongoing critical scrutiny. In particular, the introduction of innovative, still insufficiently studied AI applications in medicine should ideally begin in less safety-critical domains rather than in directly clinical, diagnostic, or interventional settings. Text-based document processing and language-oriented interactions offer a suitable entry point for today's comparatively rudimentary language-model–based systems, before more advanced and higher-risk clinical applications are *considered*. If implemented responsibly, the medical use of such powerful tools may represent a justified and meaningful application of these otherwise abstract and complex systems, despite their potential for unforeseen consequences. AI-driven technologies are unlikely to replace the human dimension of informed consent but may serve as valuable complements to physician-patient communication, particularly in contexts where time, complexity, and emotional distress limit patients' ability to process information.

Recent research supports this direction: several pilot studies have shown that AI-enhanced or multimedia-based consent tools can increase comprehension, reduce anxiety, and improve patient satisfaction, maybe even in high-stakes clinical trial settings (e.g., Rowbotham et al., 2013; Kraft et al., 2017). These findings support the notion that enhancing consent procedures with interactive technologies may address some of the structural and cognitive barriers that impede informed decision-making in clinical research, particularly when dealing with complex or emotionally charged scenarios such as oncology trials. Nonetheless, such tools must remain embedded in human-centered care frameworks and aligned with ethical principles such as autonomy, beneficence, and non-maleficence. (75,76)

More recently, LLM-based, "AI-assisted" approaches have focused on improving the text of consent materials rather than building interactive systems. In a large retrospective analysis, Mirza et al. linked higher reading-grade levels in trial consent forms to higher dropout and showed that large language model (LLM) simplification can lower reading level while preserving medico-legal sufficiency under expert review. Ali et al. similarly report that a GPT-4-assisted, expert-reviewed workflow can reduce reading level and produce procedure-specific consent forms that pass structured legal/clinical review. Together, these studies illustrate how AI can support readability and standardization, even before fully adaptive, conversational tools are deployed. (28,32)

At the same time, these studies do not yet test patient-specific personalization or real-time dialogue based on patient behavior or comprehension: the 2024 AI-assisted studies applied LLMs to rewrite or generate consent text and were judged by clinicians/legal reviewers rather than deployed in live, participant-facing interactions, and the earlier multimedia RCTs relied on tablet/web modules with linear videos, slideshows, and pre-scripted quizzes/navigation. These underlying technologies are rudimentary compared with what next-generation AI may offer (e.g., conversational agents with real-time tailoring, multimodal feedback, …). Thus, while the evidence base for multimedia and AI-assisted drafting is encouraging, the next step is to evaluate interactive, personalized consent experiences, paired with human oversight, against these baselines. (28,32,75,76)

As such, these interventions represent only an early glimpse into what may become possible with modern generative AI and context-aware systems. Tools capable of dynamic, empathic dialogue, live content adaptation, and multimodal explanation (e.g., combining visuals, speech, and text) could radically transform the informed consent process, potentially achieving levels of personalization, accessibility, and engagement that were *previously unattainable*.

Table 7: Functional Comparison of Early Multimedia-Based Informed Consent Interventions and the Capabilities of Emerging AI Technologies

Feature	**Multimedia RCTs (e.g., Rowbotham 2013; Kraft 2017)** (75,76)	**LLM-assisted drafting (e.g., Mirza 2024; Ali 2024)** (28,32)	**Modern and Future AI Models**
Primary approach	Video/slideshow/quiz; tablet/web delivery	Text simplification or de-novo drafting with GPT-4; clinician/legal review	Conversational agents; adaptive explanations driven by AI
Interactivity	Predefined buttons, linear videos, basic navigation	None	Free-form dialogue, real-time adaptation, conversational agents
Personalization	Limited (e.g., simplified language, standard visuals)	None	Dynamic adaptation to user knowledge, language, and emotional state
Media Types	Mostly video and static text	Text	Multimodal: text, speech, animation, interactive visuals, simulations
AI Technology	Usually, none or very basic scripting	Generative LLM for drafting	Generative AI, advanced NLP, context-aware, and affect-aware systems
Responsiveness	"One-size-fits-all presentation"	None	Individualized responses and clarification in real time
Time burden	- Rowbotham: Increased total session time (22.7 min vs 13.2 min) - Kraft: Did not compare total time burden	Reading time not measured; lower reading grade level likely reduces reading burden	Prospective goal: shorter or equal time via tailored explanations + teach-back
Outcome focus	Comprehension/ satisfaction (randomized comparisons)	Readability improvement; expert adequacy review; observational association with study dropout	Personalized comprehension checks, teach-back, and audit trails
Evaluation design	Randomized comparisons in patients	Retrospective dataset + expert review (no participant exposure to LLM output in some studies)	Prospectively: e.g., user studies/RCTs

Early multimedia interventions improved participant comprehension compared with text-only consent, although they can add session time. Recent LLM-assisted approaches mainly improve readability and standardization. The next step could be to test fully interactive, patient-specific consent supported by conversational AI, under human oversight, and track both comprehension and time burden.

5. Conclusion

This thesis demonstrates that regulatory frameworks, particularly the GDPR, exert a stronger influence on the structure and length of informed consent forms than trial phase or national templates. While harmonization efforts may have reduced phase-specific differences, legal requirements often overshadow patient-centered risk communication. The findings highlight that merely adding content does not necessarily improve comprehension; instead, concise language, standardized risk–benefit framing, and clear data protection sections are essential for meaningful informed consent.

Furthermore, for critical information that has the potential to prevent therapeutic misconception and common misunderstandings, a higher degree of redundancy in ICFs appears warranted compared to what was observed in the reviewed forms. Strategic repetition, particularly through explicit risk–benefit comparisons or dedicated summary sections, can ensure that the most relevant points, which numerous studies have shown are often not understood or retained by participants, are reinforced and more prominently emphasized. (54,72,73)

In this regard, not only the amount of content but also its presentation matters: visual aids, clear "navigation markers," and modular layouts in both "individualized" paper documents and digital user interfaces, as emphasized by Article 12 GDPR's call for information to be *concise, transparent, and easily accessible*, can serve as cognitive anchors that guide participants to essential information without overwhelming them. (18)

Future advanced artificial intelligence (AI) language models could offer additional potential for tailoring ICFs, for example, by simplifying technical language, generating *patient-specific* content and summaries, and ensuring alignment with readability standards. However, digitization should not create new barriers: participants must retain the option to access and sign consent forms without being forced to rely on digital tools or interactive platforms. Instead, digital enhancements should complement (rather than replace) traditional paper and/or conversation-based approaches, ensuring inclusivity across diverse literacy levels, age groups, and technical skills, while responsibly leveraging technology to improve clarity and trust.

From a practical perspective, these findings call for sponsors, ethics committees, and regulatory authorities to focus less on the sheer volume of disclosed information and more on clarity, modularity, and standardization. The use of visual elements, structured summaries, and standardized data protection language could substantially reduce cognitive burden and support a genuinely informed consent process. To bridge the gap between regulatory compliance and participant understanding, future initiatives should emphasize modular document designs, visual aids, and readability-oriented templates.

In parallel to "precision medicine", consent should move toward "precision communication". Just as medicines are increasingly tailored to pharmacogenetic profiles, the consent process should be tailored to individual participants and their attributes, accounting for health literacy and numeracy, language, sensory and cognitive needs, cultural values, risk preferences, and emotional state. In practical terms, this implies layered, modular information with optional repetition of key points, multi-format delivery (text, audio, visuals), and structured clinician/AI dialogue/teach-back to confirm understanding. Such personalization operationalizes the ethical principle of "respect for persons" and aligns with GDPR's requirement that information be concise, transparent, and easily accessible, as well as with patient-focused development principles in clinical research. The aim is not more text, but the right information, in the right form, for the right person. (11,18)

Finally, the concept of cumulative risk exposure (KRE) proposed in this thesis could further enhance ethical risk assessment by providing a broader population-level perspective. These insights may inform both regulatory updates and the design of next-generation, patient-centered ICF templates that combine legal compliance with genuine accessibility and fulfill the ethical duty to ensure that every participant has a fair capability to be adequately informed and to decide freely.

6. List of Figures

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8. List of Abbreviations

AI	Artificial Intelligence
AKEK	Arbeitskreis Medizinischer Ethik-Kommissionen
AMG	Arzneimittelgesetz
AT	Austria
CFR	Code of Federal Regulations
ChatGPT	Chat Generative Pre-trained Transformer
CI	Confidence Interval
CNS	Central Nervous System
CRO	Clinical Research Organization

CTAG	EU Clinical Trials Coordination and Advisory Group
CTIS	Clinical Trial Information System
CTML	Cognitive Theory of Multimedia Learning
CTR	Clinical Trial Regulation
DE	Germany
DSGVO	Datenschutz-Grundverordnung
e.g.	exempli gratia
ECS	Ethics Committee System
EEA	European Economic Area
eIC	Electronic Informed Consent
EK	Ethikkommission
EMA	European Medicines Agency
etc.	et cetera
EU	European Union
EUCT	European Union Clinical Trials
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FERCAP	Forum for Ethical Review Committees in the Asian and Western Pacific Region
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
i.e.	id est
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
JAMA	Journal of the American Medical Association
LLM	Large Language Model
M	Median
NLP	Natural Language Processing
OHRP	Office for Human Research Protections
PDF	Portable Document Format
PRO	Patient-Reported Outcomes
RCT	Randomized Controlled Trial
SDM	Shared Decision Making
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
SIS/ICF	Subject Information Sheet/Informed Consent Form
USA	United States of America
WHO	World Health Organization
WMA	World Medical Association
WOCBP	Women of childbearing potential

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Vienna, [03.09.2025] Jakob Gratzl

Declaration of Authorship

I hereby declare that I have written this Master's thesis independently and without unauthorized assistance. All sources, materials, and contributions of other persons have been fully and properly acknowledged.

I further declare that this thesis has not been submitted, either in whole or in part, for the award of any other academic degree at the University of Vienna or any other institution.

I am aware that any false declaration may have legal consequences.

Vienna, [03.09.2025]

10. Appendix

10.1. Supplementary Material of Experiment 1

Metadata:

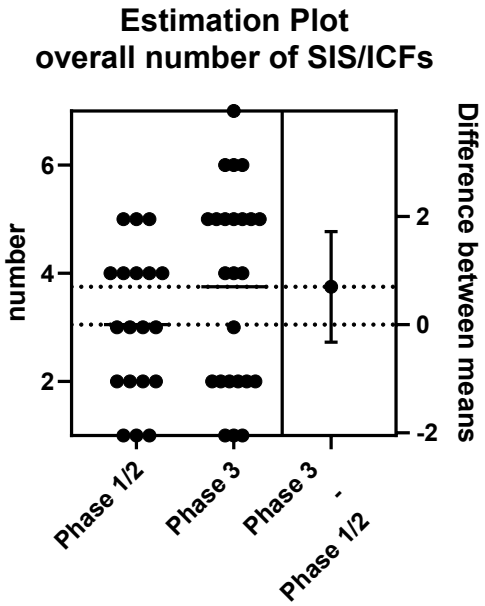

Figure 10.1: Comparison of the overall number of Study Information SIS/ICFs per clinical study between Phase 1/2 and Phase 3 trials. The estimation plot displays the mean number of SIS/ICFs per study in each group. Phase 3 trials included, on average, more SIS/ICFs (mean = 3.75) than Phase 1/2 trials (mean = 3.05). An unpaired two-tailed t-test was conducted to compare the means between groups. The difference in means was 0.697 ± 0.506 (95% CI: -0.325 to 1.720), which was not statistically significant ($t(41) = 1.377$, $p = 0.176$, $\eta^2 = 0.044$).

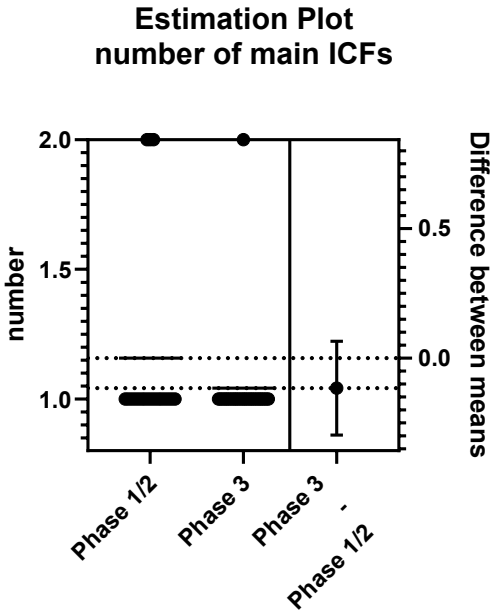

Figure 10.2: Comparison of the number of main ICFs used per clinical trial in Phase 1/2 (n=19) versus Phase 3 trials (n=24). Each dot represents one trial. The unpaired two-tailed t-test revealed no statistically significant difference between the two groups ($t = 1.298$, $df = 41$, $p = 0.2014$). The average number of main ICFs was 1.16 for Phase 1/2 and 1.04 for Phase 3 trials. The 95% confidence interval for the mean difference ranged from −0.2970 to 0.0646.

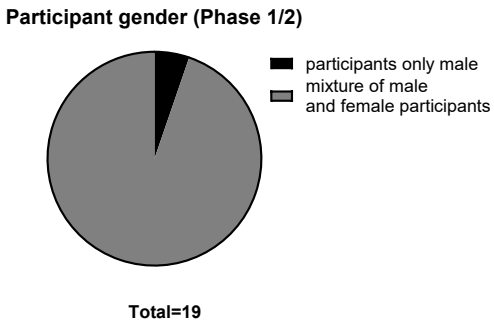

Figure 10.3: Participant gender in Phase 1/2 SIS/ICFs.

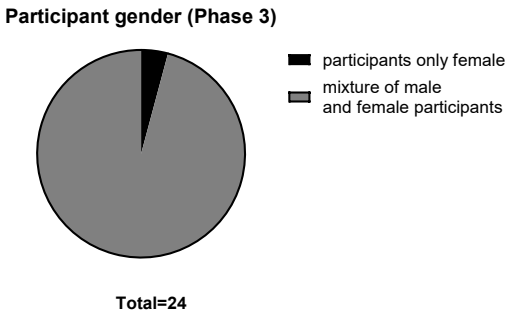

Figure 10.4: Participant gender in Phase 3 SIS/ICFs.

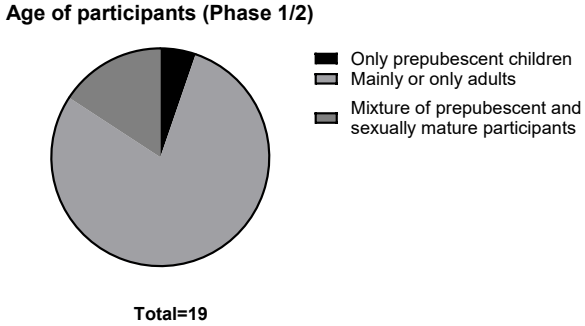

Figure 10.5: Age of participants in Phase 1/2.

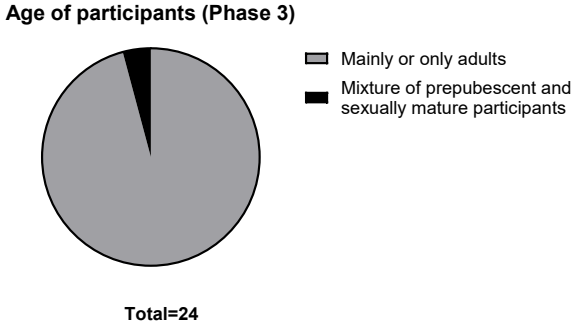

Figure 10.6: Age of participants in Phase 3.

Benefit section:

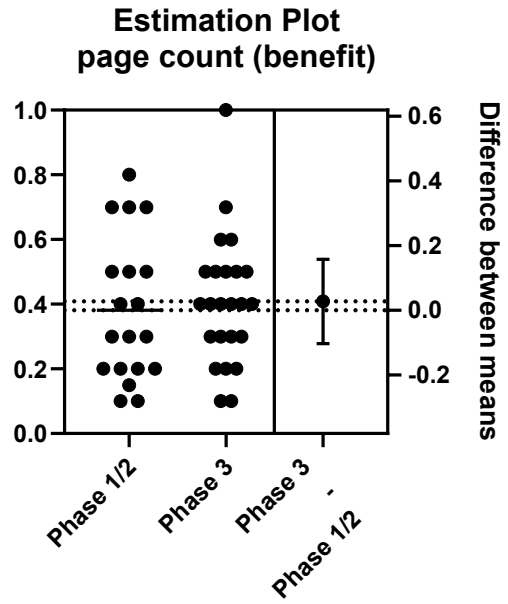

Figure 10.7: Estimation plot of benefit section page counts in Phase 1/2 vs. Phase 3 clinical trials. Each dot represents one trial. The difference in means (±95% CI) is displayed on the right. No statistically significant difference was found.

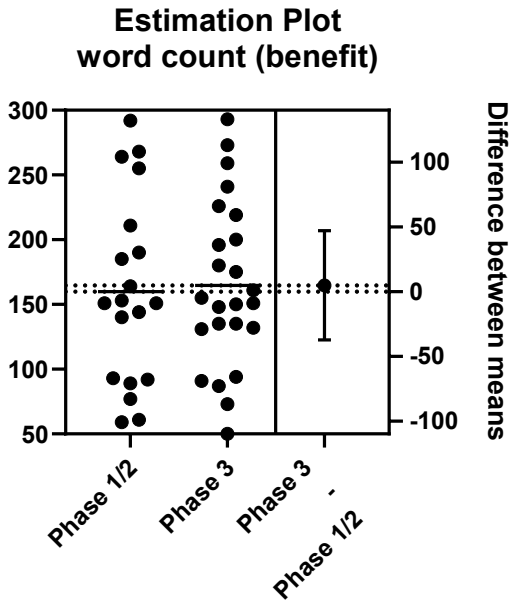

Figure 10.8: Estimation plot of benefit section word counts in Phase 1/2 vs. Phase 3 clinical trials. Each dot represents one trial. The difference in means (±95% CI) is displayed on the right. No statistically significant difference was found.

To explore whether Phase 3 trials tend to provide longer benefit-related information compared to Phase 1/2 trials, both the page count and word count of benefit sections were analyzed. Estimation plots were generated for both metrics. The mean number of pages for Phase 1/2 trials was 0.38, and for Phase 3 trials 0.41, with no statistically significant difference between groups (mean difference: 0.027 ± 0.064; 95% CI: −0.103 to 0.157; p = 0.680; R^2 = 0.004). Similarly, the average word count was 159.9 for Phase 1/2 and 164.8 for Phase 3, again without a statistically significant difference (mean difference: 4.84 ± 20.9; 95% CI: −37.4 to 47.1; p = 0.818; R^2 = 0.0013). Thus, no meaningful difference in benefit section length was observed between phases.

Pregnancy risk description:

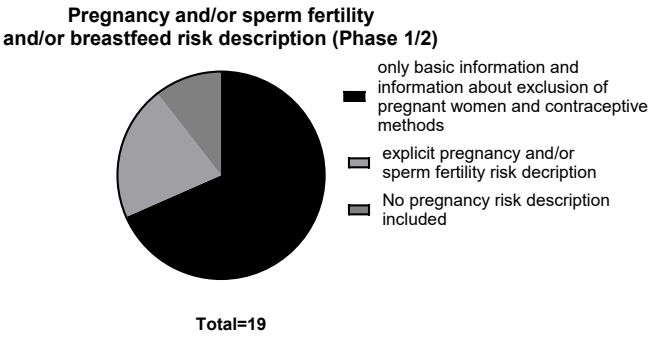

Figure 10.9: Degree of detail in the description of pregnancy-, fertility-, or breastfeeding-related risks in SIS/ICFs from Phase 1/2 clinical trials.

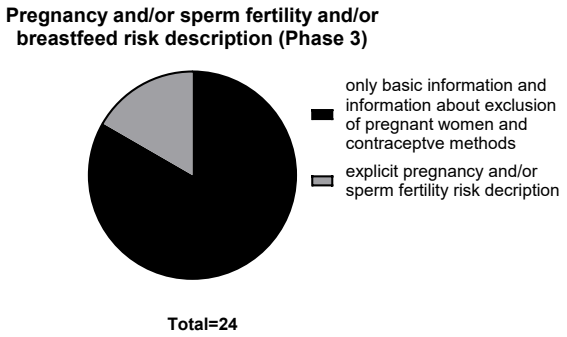

Figure 10.10: Degree of detail in the description of pregnancy-, fertility-, or breastfeeding-related risks in SIS/ICFs from Phase 3 clinical trials.

10.2. Supplementary Material of Experiment 2

Metadata:

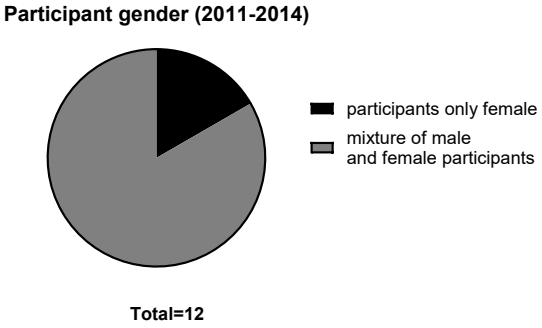

Figure 10.11: Distribution of participant gender as reported in SIS/ICFs released between 2011 and 2014. The chart categorizes whether studies included male participants, female participants, or both.

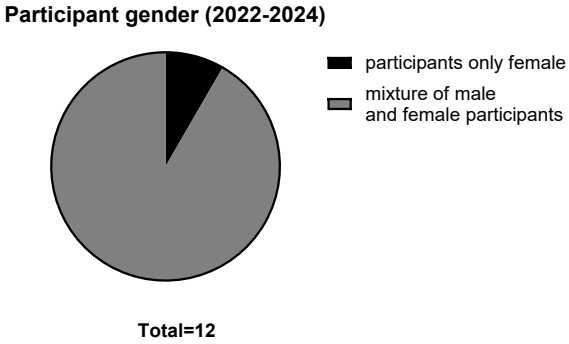

Figure 10.12: Participant gender in SIS/ICFs from 2022–2024.

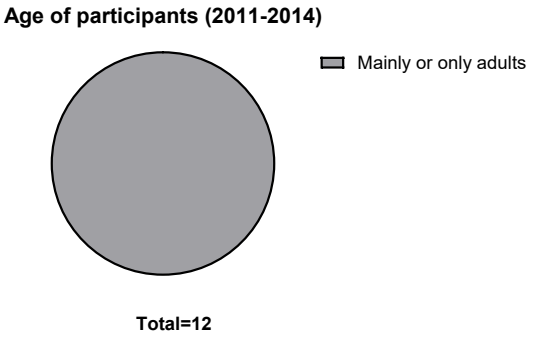

Figure 10.13: Age categories of eligible participants as described in SIS/ICFs from 2011 to 2014.

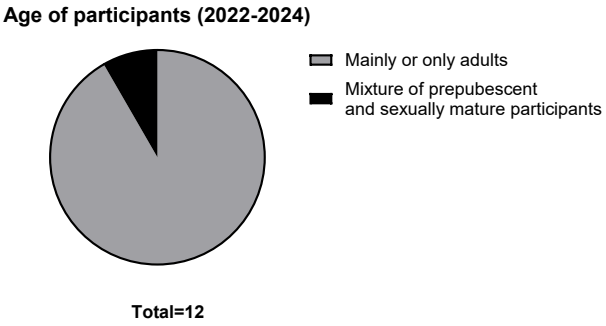

Figure 10.14: Age categories of eligible participants in SIS/ICFs from 2022 to 2024.

Risk section:

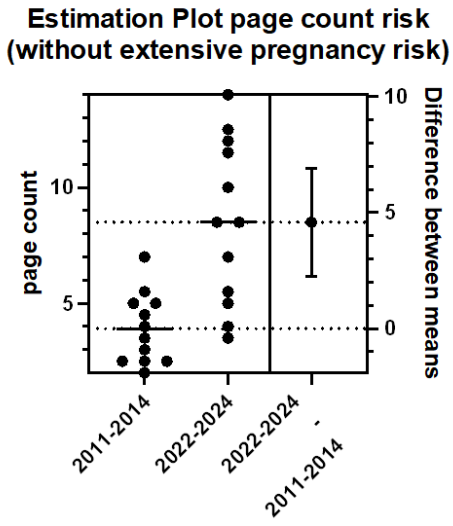

Figure 10.15: Comparison of the number of pages dedicated to the risk section (excluding extensive pregnancy-related information) in SIS/ICFS from 2011–2014 and 2022–2024 ($t(22) = 4.113$, $p = 0.0005$). On average, the newer documents included 8.5 risk-related pages compared to 3.9 in the earlier group, yielding a mean difference of 4.58 pages (± 1.11 SEM, 95% CI: 2.27 to 6.89). The effect size was large ($\eta^2 = 0.4347$).

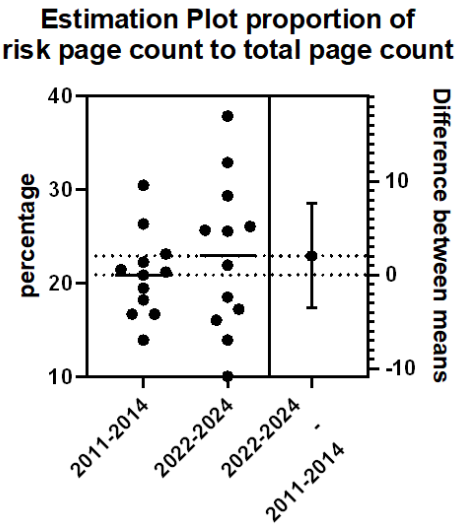

Figure 10.16: Proportion of risk section pages relative to total page count in ICFs. Comparison of the relative length of the risk section (in % of total pages) between ICFs from 2011–2014 and 2022–2024. No statistically significant difference was observed between the groups ($p = 0.460$).

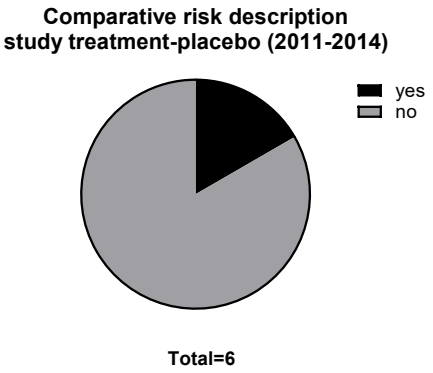

Figure 10.17: Proportion of ICFs from 2011-2014 trials that included a placebo or sham procedure in the study design (n = 6), which also provided a comparative risk description between the investigational treatment and the placebo. One of six included such a comparative description. All six ICFs contained a placebo risk description (but most of the time outside of the risk section).

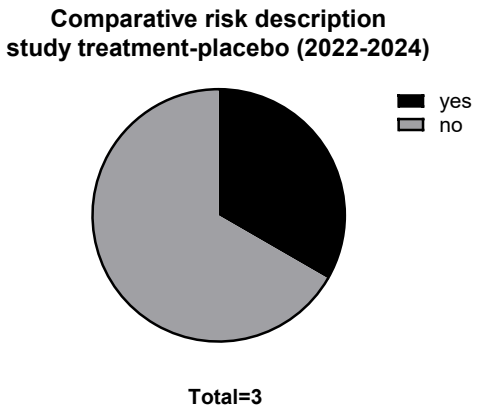

Figure 10.18: Proportion of ICFs from 2022-2024 trials with placebo or sham procedures (n = 3) that contained a comparative risk description. All three ICFs contained a placebo risk description.

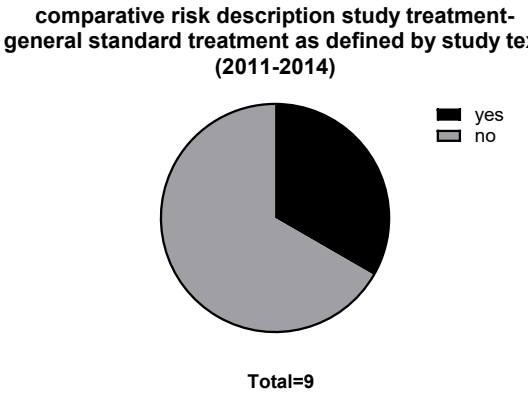

Figure 10.19: Pie chart showing the proportion of informed consent forms (ICFs) from 2011-2014 studies that included a comparative risk description between the investigational treatment and the standard treatment, in cases where a standard treatment was available and not explicitly excluded. 3 of 9 ICFs provided such a comparison.

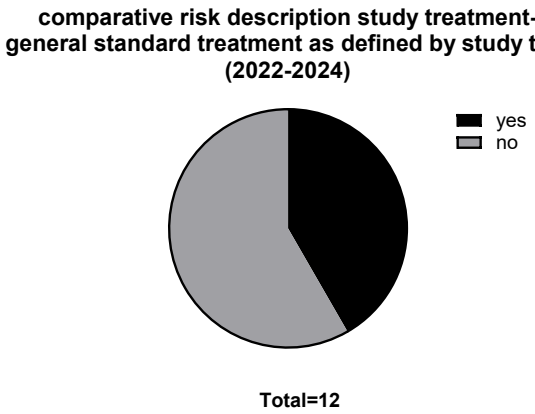

Figure 10.20: Pie chart illustrating the share of 2022-2024 ICFs that contained a comparative risk description between the investigational treatment and standard treatment, in cases where a standard treatment was available and not explicitly excluded.

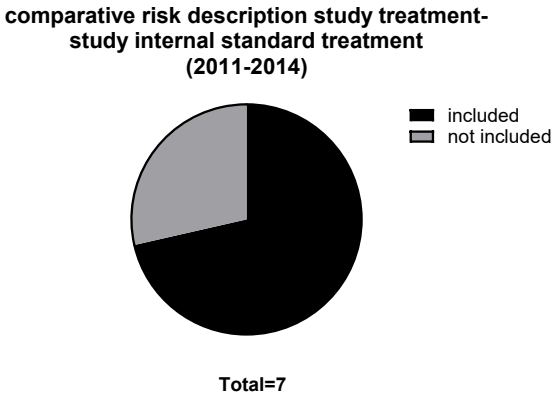

Figure 10.21: Comparative risk description between study treatment and study-internal standard treatment in 2011-2014 trials. Only trials with an internal standard treatment arm were included in this analysis (n=7). The pie chart illustrates how many informed consent forms (ICFs) provided a comparative risk description between the investigational treatment and the study's own standard treatment arm. A clear majority (71%) of these ICFs included such a comparison to some extent.

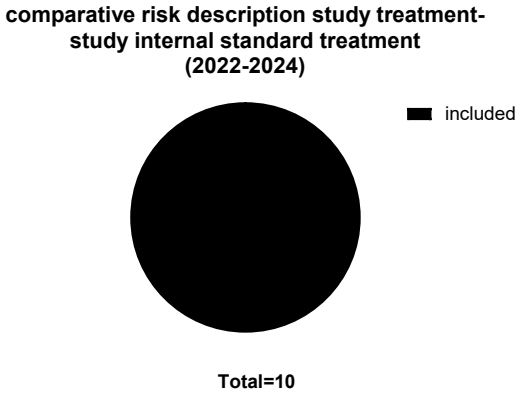

Figure 10.22: Pie chart showing that of 10 studies from the time period 2022-2024 that included a standard treatment arm 100% also included a comparative risk description between the investigational treatment and the study's own standard treatment arm.

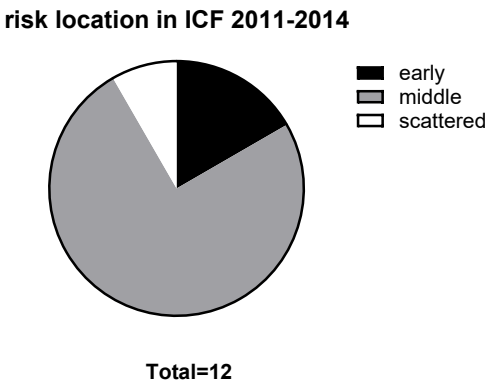

Figure 10.23: Position of the risk section within informed consent forms (ICFs) from 2011–2014. The majority of risk sections (9 out of 12) were placed in the middle part of the documents. A minority appeared early or were scattered throughout the form

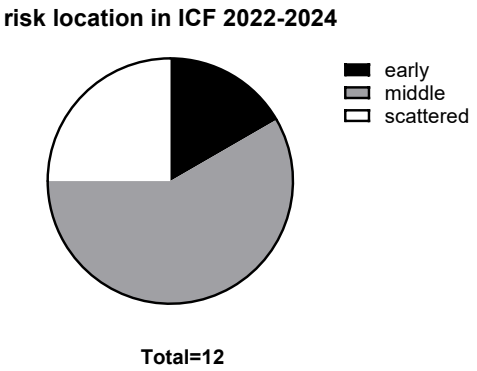

Figure 10.24: Position of the risk section within informed consent forms (ICFs) from 2022–2024. In this later period, the middle section remains the most common location for risk information, although more ICFs began placing it earlier in the document or distributing it throughout.

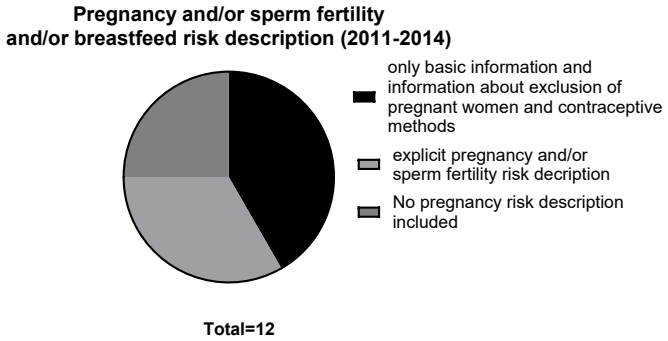

Figure 10.25: Categorization of how clearly pregnancy-related risks (including fertility, contraception, and breastfeeding) were described in SIS/ICFs released between 2011 and 2014.

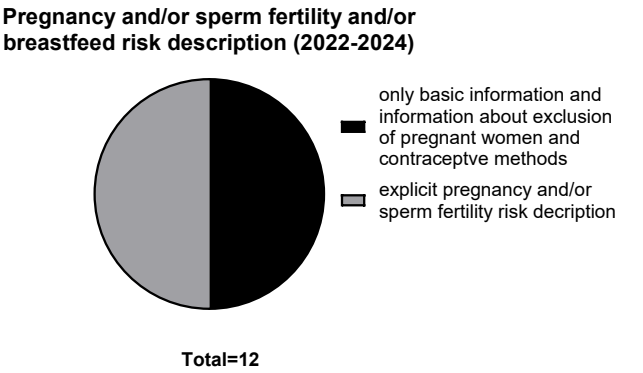

Figure 10.26: Categorization of how clearly pregnancy-related risks were described in SIS/ICFs released between 2022 and 2024. Compared to earlier documents, more recent SIS/ICFs showed a higher proportion of clearly specified content.

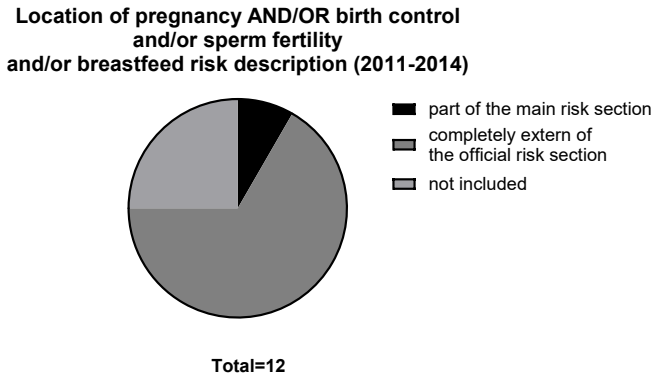

Figure 10.27: Distribution of where pregnancy-related risks and safety information (e.g., fertility, contraception, breastfeeding) were placed within SIS/ICFs from 2011 to 2014.

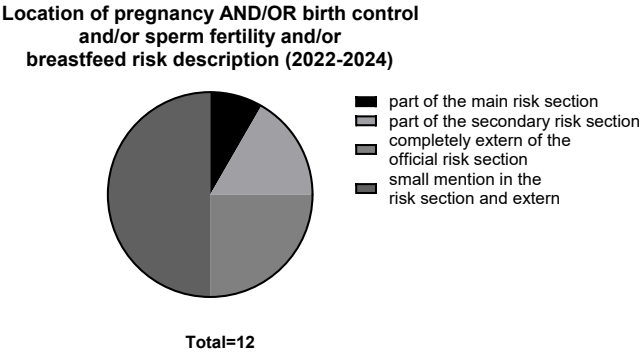

Figure 10.28: Location of pregnancy-related information in SIS/ICFs from 2022–2024.

Benefit section:

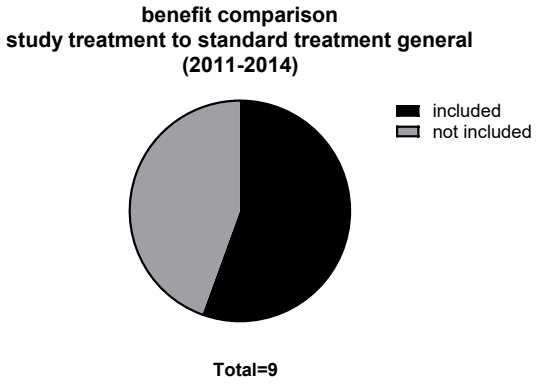

Figure 10.29: Benefit comparison with general standard treatment (2011-2014 period). Proportion of ICFs in which the study treatment was compared to a general standard treatment with regard to benefit. ICFs were only included if a standard treatment was available and not explicitly ruled out.

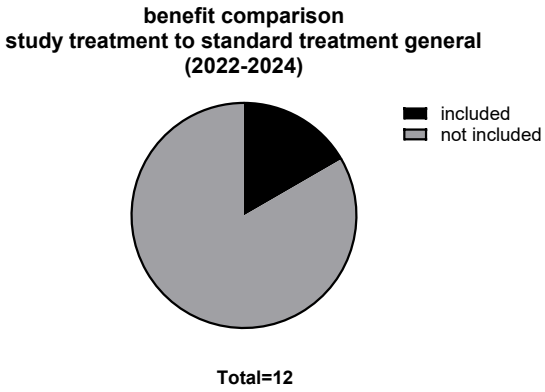

Figure 10.30: Benefit comparison with general standard treatment (2011-2014 period). Proportion of ICFs in which the study treatment was compared to a general standard treatment with regard to benefit. ICFs were only included if a standard treatment was available and not explicitly ruled out.

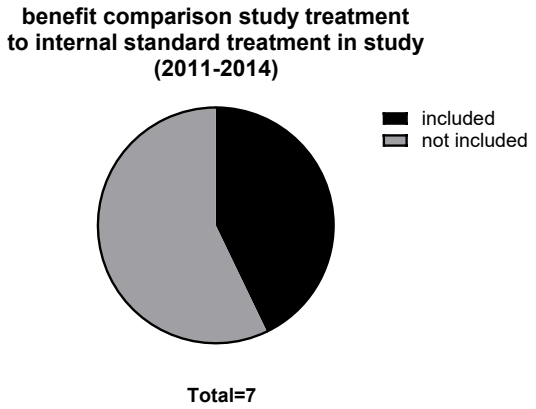

Figure 10.31: Proportion of 2011-2014 period SIS/ICFs in which a benefit comparison between the study treatment and internal standard treatment was explicitly included, in trials that featured a control arm with standard therapy (n = 7).

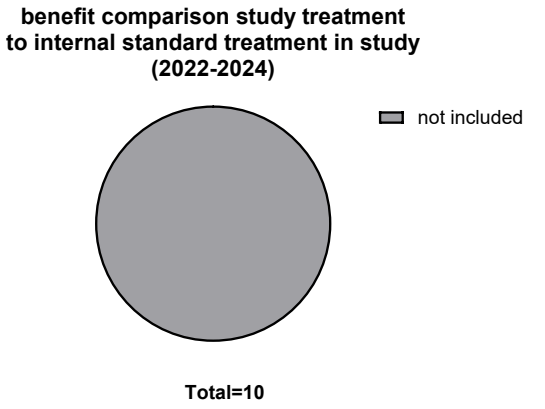

Figure 10.32: Proportion of 2022-2024 period informed consent forms (ICFs) in which a benefit comparison between the study treatment and internal standard treatment was explicitly included, in trials that featured a control arm with standard therapy (n = 10).

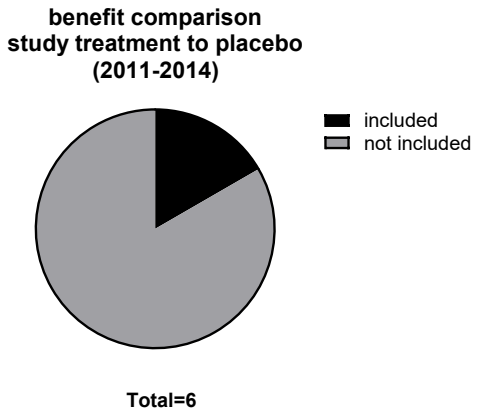

Figure 10.33: Proportion of 2011-2014 period informed consent forms (ICFs) from trials including a placebo arm (n = 6) that explicitly contained a benefit comparison between the study treatment and placebo.

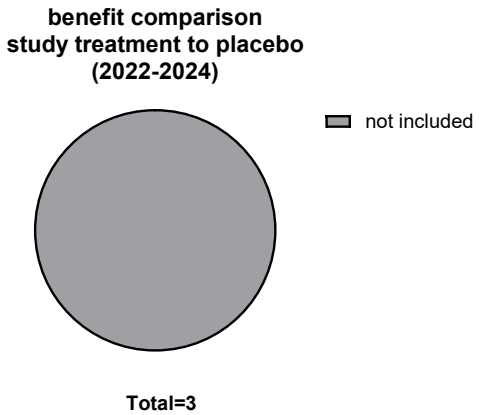

Figure 10.34: Proportion of 2022-2024 period informed consent forms (ICFs) from trials including a placebo arm (n = 3) that explicitly contained a benefit comparison between the study treatment and placebo.

10.3. Comparative Overview of Standardized ICF Templates

This section summarizes key characteristics of national and international informed consent form (ICF) templates and guidance. The table outlines structural, linguistic, and regulatory features that contribute to standardization across jurisdictions. Templates used in Austria and the EU are derived from the Clinical Trials Regulation (EU) No. 536/2014. FDA documents are included as guidance rather than structural templates. The table highlights shared features in layout, language, and standardization, supporting the main text's discussion on harmonization effects and document length saturation in later-phase multinational trials. The table includes both mandatory templates and widely used guidance models. Categorization is based on functional jurisdiction and intended application, not on legal enforceability alone.

Table 8: Comparison of National and International Informed Consent Templates and Guidance Documents

Template	Source / Jurisdiction	Structural Features	Clarity / Visual Aids	Standardization / Legal Role
Global				
SIDCER Template (40)	SIDCER: global initiative originally launched by FERCAP (Forum for Ethical Review Committees in the Asian and Western Pacific Region). Although SIDCER originated as an Asia-focused initiative to strengthen research ethics committees, its informed-consent template was designed to be globally applicable. Therefore, it integrates not only ICH-GCP and the Declaration of Helsinki, but also U.S. regulations such as 45 CFR 46, ensuring compliance with internationally recognized standards across different regulatory settings.	Boxed layout, fixed section order, placeholders for study-specific content	Use of illustrations, simplified language, and visually organized sections	Aligned with ICH-GCP, the Declaration of Helsinki, and U.S. regulations such as 45 CFR 46, widely adopted for global ethics compliance
WHO Template (41)	World Health Organization (WHO): Provides a widely used Informed Consent Template designed to assist researchers and ethics committees in ensuring ethically sound and understandable consent processes, especially in global and cross-cultural contexts.	Two-part format: Information Sheet + Consent Certificate	Designed for 6th–8th grade level; simple question-driven language	Adaptable worldwide; designed as a generic template to ensure basic ethical compliance across diverse jurisdictions
Regional				
EU Template (38)	While the authorship is not formally attributed, the template is endorsed by the EU Clinical Trials Coordination and Advisory Group (CTAG), a body responsible for promoting harmonized trial procedures across Member States. It supports the harmonized implementation of Regulation (EU) No. 536/2014 by endorsing templates, issuing guidance, and coordinating national regulatory practices.	Standardized headings for procedures, roles, and privacy; supports multilingual use	Plain language; privacy clarity; adaptable to local regulatory needs	Core implementation tool for Regulation (EU) No. 536/2014; enforces GDPR compliance for data protection.
FDA Guidance (USA) (46)	U.S. Food and Drug Administration (FDA): Federal agency responsible for regulating clinical research in the United States. Its role includes ensuring the ethical conduct of human subject research under its jurisdiction, including the protection of participants through informed consent.	Checklist-like guidance; no strict layout; focuses on required content	Recommends 8th-grade readability; separates research purpose from clinical care	Binding guidance reviewed by IRBs; no formal national template
National				
AMG Mustertext (39)	Arbeitskreis Medizinischer Ethik-Kommissionen (AKEK): National coordination body for German medical ethics committees that issued the official template for informed consent under the German Arzneimittelgesetz (AMG), version 1.2, adopted on 25.11.2022. The template is widely used for ethics submissions in Germany and reflects regulatory, ethical, and linguistic standards for drug trials.	Modular sections (e.g., risks, voluntariness, data protection); legally fixed structure	Formal, concise phrasing; integrated GDPR wording	Required by German ethics committees; based on national Arzneimittelgesetz (AMG)
Standardvorlage für CTR-konforme klinische Prüfungen (37)	Forum der österreichischen Ethikkommissionen: Provides a harmonized informed consent template for clinical trials conducted in Austria under Regulation (EU) No. 536/2014. The template reflects national ethical and legal requirements (e.g., § 40 AMG, GDPR) and is widely used in ethics submissions to ensure consistency across Austrian trial sites.	Based on EU CTR; includes optional modules and summary for forms >10 pages	Preset wording; clear layout	Official template for Austrian clinical trials under EU CTR Frequently references legal bases (§ 40 AMG (Austrian Arzneimittelgesetz), DSGVO (GDPR), Regulation (EU) No. 536/2014.