CLINICAL RESEARCH IN EUROPE: PUTTING QUALITY AND PATIENT SAFETY FIRST

Recommendations by the Coalition for Reducing Bureaucracy in Clinical Trials

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EXECUTIVE SUMMARY

Accumulating administrative burdens put at risk the quality of clinical trials and the safety of patients. Investigators are overwhelmed by legal, regulatory and sponsor requirements to the extent that they struggle to focus on what really matters: the safety, efficacy, and effectiveness of a treatment. Patients are confronted with informed consent forms and procedures that often are hard to understand, and that tend to be compliance rather than patient centric.

Since 2020 a broad cross-disciplinary coalition of medical societies and patient advocates has been calling on regulators, policymakers, sponsors, Ethics Committees and other stakeholders in making clinical trials less bureaucratic and more efficient and patient-centred. With the needs of investigators and patients as starting point, whilst taking into account stakeholders' views and interests, the Coalition for Reducing Bureaucracy in Clinical Trials developed a first set of recommendations in 2021.

Encouraging responses to these recommendations from many in the clinical trials ecosystem, combined with the early lessons from the implementation of the EU's Clinical Trials Regulation (in effect since January 2022) and growing concerns about the EU's global competitiveness in clinical research, offered additional inspiration for formulating the more elaborate set of 'Coalition Recommendations' presented in this document. It is structured in three parts – Regulatory, Safety Reporting, and Informed Consent – with appended clarifications and two simplified, patient-friendly, highly fit-for-purpose Informed Consent Form templates developed by patient advocates in close collaboration with clinicians and ethics experts.

Recommendations for aligning and harmonizing the EU regulatory framework

Navigating multiple regulatory frameworks and requirements places a considerable administrative burden on academic investigators and sponsors. Consequently, they often prioritize conducting clinical trials in countries where sufficient patient recruitment is feasible within a single regulatory system – or, as is happening increasingly in academic research, opt not to initiate the trial at all. To make multinational trials in smaller EU Member States with different regulatory regimes more attractive to sponsors – and ultimately expand access to innovative clinical trials for European patients – greater harmonisation of clinical trial processes across the EU is urgently needed.

This section outlines specific solutions aiming for more streamlined, coordinated, and time-efficient clinical trial assessments, by means of regulatory harmonisation. These include supporting the improvement and wider adoption of the Reporting Member State-led assessment introduced by the Clinical Trials Regulation (CTR), as well as the standardization of templates across Member States.

We also propose targeted recommendations to enhance proportionality in regulatory requirements – for instance, adapting safety reporting obligations according to the level of risk. More risk-proportionate approaches to safety reporting would substantially reduce the administrative burden on investigators. Finally, we address areas of ambiguity within the CTR and suggest the development of AI-powered tools to provide investigators with reliable, targeted guidance on regulatory queries.

Recommendations for streamlining and rationalizing safety reporting

Major inefficiencies in safety reporting procedures place a considerable strain on investigators. This contributes to burnout and makes the role of investigator less appealing, as doctors see bureaucratic demands encroaching on the time they would rather dedicate to research and patient care – the core motivations for choosing a career in clinical research. To help reverse the negative impact of bureaucracy on the workforce crisis, key issues in safety reporting must be addressed.

A major challenge is the duplication of reporting: adverse events must be recorded in hospital records, entered into the sponsor's or the CRO's electronic data capture (EDC) system, and – if serious – submitted again through the sponsor's safety reporting platform for expedited reporting. The lack of a centralized EU safety reporting platform further complicates this process, forcing sponsors to implement their own systems and requiring investigators to navigate multiple platforms across different trials. Moreover, when sponsors do not list disease-related serious adverse events (SAEs) in the protocol or fail to implement a periodic process for aggregating and analysing suspected unexpected serious adverse reactions (SUSARs), investigators are left to report non-informative SAEs and manage an excessive volume of individual SUSAR notifications – potentially obscuring critical safety signals. This section offers practical solutions, aligned with the Clinical Trials Regulation (CTR), to help sponsors streamline safety reporting and reduce unnecessary burdens on investigators.

Recommendations for more inclusive and patient-centred informed consent

Patients often find Informed Consent Forms (ICFs) difficult to read and understand. This is largely due to their length, the use of technical language, and a strong focus on legal compliance, which results in the frequent inclusion of complex legal text. These factors can negatively affect patient participation and equitability. In this section, the Coalition offers practical solutions to make ICFs more patient-centred.

One recommendation is to move detailed legal language to an appendix, while including a legally valid summary – written in plain, accessible language – in the main body of the form. This approach allows patients to grasp the essential information without being overwhelmed, while still having the option to consult the full legal text if they wish. Additionally, we have developed two ICF templates based on these principles and gathered patient feedback on them. The insights collected aim to support sponsors and Ethics Committees in designing and assessing more inclusive and understandable consent forms.

The goal

These Coalition Recommendations aim to provide short and medium-term solutions that are pragmatic, concrete, and feasible. They do not seek to eliminate all 'bureaucracy', not everything that is 'burdensome'; they target those rules and requirements that do not serve the quality and effectiveness of clinical trials, that do not contribute to enhancing patients' safety and access to innovative treatments.

The recommendations are complementary and comprehensive: it is through their combined uptake and impact that they can contribute substantially to diminishing administrative burdens.

When implemented together, with broad commitment and serious effort by all in the ecosystem, they will provide much-needed relief to investigators, make clinical trials in Europe easier to conduct as well as better and more patient-centric, and improve the efficiency and attractiveness of Europe as the place-to-be for high-quality clinical research that is of added value to all involved – patients above all.

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INTRODUCTION

'Reducing bureaucracy in clinical trials: now is the time!' was the title of a statement issued in 2020 by a broad cross-disciplinary coalition of medical societies and patient advocates. Expressing concern about the impact of accumulating administrative burdens – which put at risk the quality of clinical trials, access to innovative treatments, and patient safety – the statement called on regulators and other stakeholders to collaborate to make trials less bureaucratic and more efficient and patient-centred.

The Coalition for Reducing Bureaucracy in Clinical Trials ('the Coalition') set out to develop a first series of concrete and consensus-based recommendations (November 2021), clustered around four main themes: safety reporting, informed consent, regulatory guidelines, and harmonisation of requirements across the European Union. Whilst these represented the views and needs of investigators and patients, the Coalition has actively sought dialogue with and input from policymakers, regulators, sponsors, Ethics Committees and others interested in pragmatic, consensus-based, feasible solutions.

The impact of bureaucratic obstacles on both investigators and patients can be severe, by reducing time for patient care and by contributing to healthcare professionals' high burnout rate[1,2]. In combination with resource limitations, they stifle academic research and exacerbate the EU's growing shortage of healthcare professionals by making work in clinical research less attractive to younger generations. These inefficiencies also feed into a broader issue: Europe's declining share of global commercial clinical trials compared with Asia and the United States[3,4]. This trend is alarming, given the strategic importance of the life sciences sector to the EU economy and its role in ensuring timely access to innovative treatments for European patients. A major driver of this decline is the fragmentation of regulatory requirements across Member States. Unlike countries such as the US or China – where large trials can be run under a single regulatory system – the EU requires coordination across multiple jurisdictions, demanding significant investment in regulatory knowhow and legal support. Despite Europe's excellent hospitals and skilled workforce, the prolonged duration of, and inconsistent procedures for, the evaluation and approval of trials place it at a competitive disadvantage.

To help reverse the (relative) decline in the EU's share of clinical trials activity and create a more attractive environment for research, the Clinical Trials Regulation (CTR) – in force since 31 January 2022 – was introduced. A key element of the CTR is the Clinical Trials Information System (CTIS), a unified platform designed to harmonise clinical trial applications and assessments across Member States. While this marks an important step towards greater consistency and efficiency[5], the Coalition has identified issues within the CTR that could prevent CTIS from being used to its full potential. Building on the momentum of the Accelerating Clinical Trials in the EU (ACT EU) initiative – which fosters collaboration between regulators and stakeholders – we have updated and refined our recommendations to reflect these ongoing issues and to propose practical solutions. While these recommendations reflect the views and needs of investigators and patients, they have been shaped through active engagement with policymakers, regulators, sponsors, Ethics Committees and others, to ensure that the proposed solutions are feasible, enjoy broad support, and tackle barriers across the regulatory realm and beyond.

RECOMMENDATIONS

I. Regulatory

1. Harmonising clinical trial processes across the EU:

- **Streamline and align the EU clinical trial assessment framework**

Although CTIS was developed primarily to streamline the submission and assessment of multi-country clinical trial applications in Europe, the platform alone cannot achieve this goal without broader improvements to the European assessment framework. To address this, the CTR introduced a coordinated assessment of Part I of the Clinical Trial Application (CTA). Under this model, all participating National Competent Authorities still conduct their own evaluations, but under the coordination of the Reporting Member State (RMS) which drafts an initial report, incorporates feedback from other Member States, and delivers a consolidated final assessment. In practice, however, sponsors often receive unfiltered, repetitive, or even contradictory Requests for Information (RFIs) from participating Member States, indicating that the RMS may lack adequate training, support, or authority to manage the coordination process effectively. We therefore recommend that the responsible teams for performing RMS tasks in all Member States receive appropriate, uniform training.

Potential efficiency gains of the RMS-led assessment process may also be undermined by the significant differences in national approaches. For instance, while countries like the Netherlands rely solely on Ethics Committees for the entire CTA assessment, most other Member States involve their respective competent authorities, with input – either binding or non-binding – from Ethics Committees, in the Part I assessment of the CTA. The Part I documents reviewed by Ethics Committees also differ between countries, further contributing to fragmentation and inconsistency.

While the Coalition does not have a collective preference as to how Part I should be assessed – either only by Ethics Committees or by both National Competent Authorities and Ethics Committees – we recommend, as a minimum, establishing a framework that ensures alignment between the two – ensuring that, in case of dual assessment, the input of Ethics Committees is taken into account. We support multidisciplinary review teams of competent authorities and Ethics Committees that include experts in statistics, clinical research, science, and regulatory affairs, and continuous training to keep their expertise up to date.

To further enhance the efficiency of multi-country clinical trials, we propose extending the Reporting Member State (RMS)-led assessment model to include common, non-country specific parts of Part II documents of the CTA. While this proposal deviates from the current CTR (Appendix 1), the Coalition strongly advocates for enhanced collaboration and coordination among Ethics Committees, which are essential for the effective governance of clinical trials in the EU.

- **Align Informed Consent Form (ICF) requirements**

While Part I documents of the CTA are harmonised and submitted as a single version for coordinated assessment by all participating EU Member States, Part II requires separate submissions of different versions of the same documents to each participating Member State. This is because national Ethics Committees assess Part II according to their own national regulations, cultural contexts, and ethical standards – including the requirement for the informed consent form (ICF) to be provided in the local language. As a result, what is deemed acceptable in one country may not be in another, necessitating customized ICFs for each Member State. The lack of harmonisation in ICF requirements not only undermines efforts to streamline the clinical trial application process, but also to create clear, patient-friendly ICFs, which are critical for ensuring that patients fully understand the potential risks and benefits of participating in a trial.

To address this issue, the Coalition proposes a two-part structure for ICFs. The first part would contain essential elements standardised across all EU countries, such as descriptions of screening tests, potential side effects, and benefits of the trial. This section would need certified translation into the languages of all participating countries and would be subject to a coordinated assessment following the same RMS-led process used for Part I of the CTA. The second part would include country-specific details, like available treatment options – which may vary based on the standard of care in each Member State – and legal information regarding protection of personal data and storage of biological samples.

Adopting this two-part structure would facilitate the use of a unified EU template for a more patient-friendly first part of the CTA, ensuring consistency in the provision of essential information for all EU patients.

- **Establish a European fast-track mechanism for public health emergencies**

As a result of the lessons learned from clinical trials conducted during the COVID-19 pandemic, the Coalition strongly supports the ongoing development and reinforcement of key initiatives such as the Health Emergency Preparedness and Response Authority (HERA), established by the European Commission in 2021 to strengthen the EU's capacity to anticipate, detect, and respond to cross-border public health threats, and the Emergency Task Force (ETF) of the European Medicines Agency (EMA), essential for providing rapid scientific advice and regulatory support during public health crises. To further streamline clinical trial processes during public health emergencies, the Coalition also supports the establishment of a centralised European Ethics Committee that would conduct coordinated assessments in alignment with the ETF. These assessments should be binding to participating Member States, to avoid conflicting and prolonged assessments where fast initiation of trials is critical. The proposed centralized ethics and regulatory framework would enable faster, more harmonized trial implementation across the EU, ensuring better preparedness for, and management of, future pandemics.

- **Harmonise contract writing and negotiation**

Contract writing and negotiation remain critical administrative steps in the clinical trial process that would benefit from greater harmonisation across Europe. The lack of alignment, even at the national level, contributes significantly to delays in clinical trial initiation – especially in multi-country trials and in certain Member States. Some EU countries have already implemented effective solutions, such as standardised templates for which key clauses on liability, intellectual property, publication rights, and indemnification are pre-negotiated by stakeholders. In France, unlike most Member States where national association templates are optional, the use of the MR-CT (Modèle de Référence de Contrat de Recherche Clinique) template is mandated under the Convention Unique, a legal framework designed to streamline the contracting process. This has proven to significantly reduce negotiation timelines.

Introducing a common EU clinical trial agreement template, supported by modular annexes for national adaptations, could significantly streamline site-level negotiations. Furthermore, the harmonised section could eventually incorporate Data Hosting/Storage Requirements once provisions for secondary use in the European Health Data Space (see below) are fully implemented, promoting legal certainty, interoperability, and transparency. By implementing a mandatory EU contract template with predefined, limited modifications, prolonged negotiations would be reduced, allowing legal teams to focus on national and minor trial-specific adjustments. This approach would ultimately shorten clinical trial start-up timelines and ensure timely access to the best treatments for patients.

- **Facilitate direct upload of hospital records into a European database**

The establishment of a unified European online platform for safety reporting between investigators and sponsors/CROs would be a significant and feasible step toward streamlining and harmonizing processes across Member States and clinical trial sponsors. In the future, integrating direct data uploads from hospital records into a central European database – where sponsors and CROs have restricted access only to their participants' data – would further enhance efficiency. This approach would eliminate redundant data entry, reduce errors, and improve overall reporting quality. A similar framework could be established for accountability reporting by trial pharmacists, who are currently required to document detailed information on investigational medicinal products twice.

With a view to advancing such improvements, the Coalition welcomes the creation of the European Health Data Space (EHDS), based on EU legislation which entered into force on 26 March 2025. A harmonized EU electronic hospital records system based in the 'European Electronic Health Record exchange Format (EHRxF)' would significantly benefit patient mobility by facilitating seamless data exchange for primary use (patient care). Additionally, we welcome the legislation's provisions on secondary use, which will enable controlled access to high-quality, non-identifiable data for clinical research.

However, the EHDS does not address the challenges of health data collection and sharing in clinical trials. The safe and seamless exchange of patient data between investigators, CROs, and sponsors remains an unmet need in EU legislation. The Coalition urges the development of a similar infrastructure to support data-sharing within clinical trials, leveraging the EU-wide harmonized electronic hospital records system. Integrating safety reporting into the EHDS would significantly reduce the administrative weight on investigators while improving overall efficiency. The EHDS presents a unique opportunity for further harmonization across EU Member States, fostering collaboration in clinical trials while ensuring compliance with European data protection standards.

2. Improving proportionality in regulatory requirements and the application process:

- **Extended definition of non-interventional clinical studies**

The CTR currently defines non-interventional studies as those where a medicinal product is prescribed in accordance with its marketing authorisation to investigate the product's effectiveness, safety, and tolerability in real-life conditions (Appendix 2). However, the Coalition considers this definition overly restrictive, as it excludes studies that pose minimal risk to participants and, therefore, should not be subject to the full regulatory requirements of traditional clinical trials. An example is a study in which treatment allocation is determined by a trial protocol or where only minor diagnostic or monitoring procedures – such as additional blood tests or imaging – are involved.

To address this limitation, the Coalition proposes broadening the definition of non-interventional studies to include trials that incorporate randomisation and minimal additional procedures, provided these do not significantly depart from normal clinical practice. For instance, randomised studies comparing approved treatments – either within their authorised indications or where substantial literature supports their use – should qualify as non-interventional when conducted within the context of standard care. In this context, randomisation should be viewed not as a medical intervention but as a methodological tool to reduce bias.

Furthermore, trials including minor diagnostic or monitoring procedures – such as an extra CT scan in oncology patients where such imaging is part of usual care – should also fall within the non-interventional category, as long as these additions are consistent with routine practice for the specific patient population.

Expanding the definition in this way would allow a broader range of low-risk, real-world studies – such as pragmatic randomised controlled trials comparing approved therapies or standard-of-care regimens – to qualify as non-interventional. This would streamline regulatory oversight, reduce the amount of unnecessary administrative requirements, and support innovation without compromising participant safety.

However, while classifying a study as non-interventional is intended to reduce administrative burden, this benefit often does not extend to multinational trials. Unlike interventional studies, which benefit from the Clinical Trials Information System (CTIS)

enabling single-submission access for all Concerned Member States, no equivalent platform exists for non-interventional studies. Sponsors must therefore submit separate applications through various national systems, significantly increasing complexity and workload.

The Coalition proposes the creation of an EU-wide platform, similar to CTIS, for multinational non-interventional studies. This would allow a single application to be submitted to all relevant national review bodies, streamlining the process and improving efficiency.

Which bodies are required to review applications for multinational non-interventional studies varies between Member States: some mandate the involvement of both Ethics Committees and National Competent Authorities and impose safety reporting obligations – even though such studies pose no more risk than routine care. While non-interventional studies fall outside the scope of the CTR, the Coalition recommends exempting them from national authority review and from safety reporting obligations beyond standard post-marketing requirements, limiting oversight to Ethics Committees.

To further harmonise procedures, an RMS-led assessment model, like the one used in interventional trials, could be introduced for Ethics Committee review of multinational non-interventional studies. This would enable consistent acceptance or rejection of the non-interventional classification and the study itself across participating countries. To support this process, a standardised EU application template for non-interventional clinical trials should be established.

In cases of disagreement between applicants and Ethics Committees on whether a study qualifies as non-interventional, the Coalition recommends consulting national medical societies for single-country studies, or European medical societies for multinational ones. These expert bodies can offer informed guidance on what constitutes normal clinical practice or Standard of Care – key in determining study classification.

Ultimately, Ethics Committees in each of the participating Member States will remain responsible for confirming that a study adheres to the Declaration of Helsinki.

By addressing these gaps, the EU can harmonise oversight of non-interventional research, reduce unnecessary administrative barriers, and foster more efficient multinational collaboration.

- **Case-by-case assessment of low-intervention clinical trials**

The CTR introduced the concept of ‘low-intervention clinical trials’ (Appendix 3) to streamline the approval process for certain trials that involve authorised drugs or therapies. These trials are defined as those that use marketed drugs (excluding placebos) in accordance with their approved indications, or where evidence-based data or published research supports the safety of the interventions. The CTR stipulates that these trials should not impose more than minimal additional risk or burden to participants when compared to standard care (Appendix 3). However, the Coalition points out that the definition of "minimal additional safety risk or burden" remains vague, creating challenges in accurately classifying trials as ‘low-intervention’.

The Coalition considers that pragmatic trials involving approved drugs and treatment modifications – such as dose reduction or discontinuation, changes in treatment duration, or combination therapies – generally pose only minimal additional risk and should therefore qualify as 'low-intervention' trials. Additionally, studies using approved drugs for off-label indications should also be eligible for this classification. While such studies may carry a potential risk of reduced efficacy in the new indication, they generally do not increase the likelihood of adverse effects. Accordingly, the Coalition supports broadening the criteria for "evidence-based justification" to include not only data from studies involving the same drug in different indications but also evidence from similar or comparable compounds.

In addition, the Coalition contends that trials involving approved drugs, even when they include additional major therapeutic or invasive procedures, could still qualify as 'low-intervention' if those procedures closely reflect normal care practices. In such cases, the definition of "minimal additional risk or burden to the safety of the subjects" should be considered context-dependent and assessed against the standard of care for the specific condition.

The Coalition recommends applying a similar assessment framework to that of non-interventional studies. Specifically, classification and oversight of low-intervention trials should rest with Ethics Committees, which must include patients and clinical research professionals with relevant therapeutic expertise. These committees are best positioned to evaluate the added burden or deviation from routine care.

However, recognising that low-intervention trials may carry a higher level of risk than non-interventional studies – due to treatment modifications and the potential inclusion of additional invasive procedures – the Coalition recommends limited additional safety reporting. Specifically, serious unexpected suspected adverse reactions (SUSARs) should be reported immediately. Serious adverse events (SAEs) should be reported on an annual basis, while non-serious adverse events should be reported only if they are of special interest or directly related to the study objectives.

Expanding the scope of what qualifies as a 'low-intervention' trial would simplify regulatory procedures and reduce administrative burden for studies posing lower risks, thereby improving access to academic-led research. This is particularly important for investigating treatment optimisation using already-approved therapies, a field often neglected by commercial sponsors[6].

- **Reducing regulatory barriers to paediatric and critical care research**

The CTR aims to ensure the safety and protection of vulnerable populations, including children and critically ill patients, participating in clinical research. However, its stringent requirements have inadvertently created significant challenges for studies involving these groups. A clear example is found in Article 32 (Appendix 4), which stipulates that clinical trials involving minors may only be conducted if they focus on treatments for medical conditions unique to minors or if data obtained from adult trials require validation in the paediatric population. In practice, this means that clinical trials for

diseases affecting both children and adults are primarily conducted in adults, with paediatric trials occurring only when additional validation is deemed necessary.

Although sponsors of adult clinical trials are required to develop a Paediatric Investigation Plan (PIP) to ensure that new medicines are appropriately researched for use in children, several barriers often hinder paediatric recruitment. These include the lower incidence of many diseases in paediatric populations, children's increased vulnerability to invasive procedures, parental preference for off-label treatments already tested in adults over therapies unproven in clinical trials, and ethical concerns about assigning children to treatment arms involving inadequate dosing or placebo. Consequently, sponsors frequently request deferrals or even waivers, leading to significant delays in paediatric approvals[7].

To address these challenges, we recommend that targeted pharmacokinetic studies, which are a less demanding alternative to full Paediatric Investigation Plan (PIP) studies, should be conducted within 6 months of the completion of the adult Phase 3 trial. In this regard, we propose that these and other paediatric pragmatic clinical trials – such as those investigating dose reduction, treatment duration, and combination therapies – be classified as low-intervention trials, provided they do not introduce significant therapeutic or invasive procedures beyond routine care. By allowing more paediatric pragmatic trials to be classified as 'low-intervention', we would reduce bureaucratic barriers, enabling small academic teams to sponsor these crucial studies that may otherwise remain unperformed.

The urgency of addressing these challenges is underscored by the 2024 revision of the Declaration of Helsinki (Appendix 5), which emphasizes the ethical responsibility of ensuring the equitable inclusion of vulnerable populations in research while safeguarding their rights and well-being.

- **Flexible deadlines for academic sponsors during the clinical trial application process**

The CTR has established clear timelines for document submission and review during the clinical trial application process. While these timelines offer a significant advantage to commercial sponsors that have dedicated regulatory teams, they present challenges for academic sponsors. Academic teams, often lacking the resources of commercial entities, may struggle to meet these stringent deadlines, which could discourage them from performing smaller, non-commercial studies. The pressure to comply with these complex processes may deter academic research groups, which are already navigating resource constraints, from engaging in clinical trials under the current regulatory framework. Without more flexibility, such as the inclusion of a 'clock-stop' option for academic sponsors, there is a real concern that these timelines could unintentionally impede academic institutions' contributions to clinical trial innovation.

- **Streamlining Patient Consent with Digital Signatures**

Patient recruitment can be a lengthy process, often delaying the start of clinical trials. One key factor contributing to delays is the requirement for patients to physically visit the trial site to provide their signed consent.

To streamline patient recruitment and reduce administrative barriers, the EU should enable verified electronic consent across all Member States, ensuring compliance with regulatory and ethical standards. Implementing an EU-wide digital consent framework with auditable digital records would significantly improve efficiency, allowing for faster, more accessible, and secure consent collection while maintaining transparency and data integrity.

3. Reducing CTR ambiguity and enhancing comprehension:

- **Clarify reporting roles for serious breaches**

The CTR contains numerous vague definitions and requirements that often lead to over-interpretation and inconsistency. A notable example is the ambiguity over who determines what constitutes a 'serious breach'. The term 'serious breach' applies to any protocol deviation or regulatory failure significantly impacting participant safety, rights, or data integrity. While sponsors must report serious breaches to regulatory authorities, the CTR lacks clarity on who makes the final call on what qualifies as 'serious', creating potential discrepancies between clinical and regulatory perspectives.

This lack of clarity can lead to inconsistencies in how breaches are identified, documented, and reported, potentially complicating regulatory oversight and diminishing accountability. To address these challenges, the Coalition underscores that no serious breach report should be submitted without the investigator's agreement. Moreover, to avoid possible conflicts of interest, three investigators should be consulted, at least two of whom would have to agree on categorising the deviation as a serious breach. A more structured approach in the CTR, with clear guidelines on the roles of sponsors and investigators in assessing and reporting serious breaches, would enhance consistency, transparency, and compliance across EU Member States.

- **Facilitate access to guidance and targeted advice on regulatory requirements**

Investigators, who need to be primarily focused on the clinical aspects of trials, are not typically trained in navigating complex regulatory requirements. Requiring them to interpret and apply detailed legal frameworks, such as the CTR with its accompanying guidance, Q&A and other support documentation, increases their workload and detracts from their core responsibilities. To mitigate this, the Coalition recommends that EMA collaborates closely with investigators to develop a user-friendly website. This platform would enable investigators to pose specific regulatory questions and receive clear, concise answers based on the CTR and related guidelines, reducing the need for extensive regulatory training. In addition, the platform could be a valuable resource if

offered in multiple EU languages, enhancing accessibility and utility across Member States. By streamlining access to regulatory guidance, this tool would simplify compliance, support investigator productivity, and ultimately contribute to a more efficient clinical trial process throughout the EU.

II. Safety reporting

To improve the quality of clinical trials and alleviate the administrative burden on clinical trial personnel - allowing them to dedicate more time to providing patient care - the Coalition has included a dedicated section in this publication focused on safety reporting. It presents specific recommendations aimed at streamlining processes and ensuring more efficient, targeted, fit-for-purpose safety oversight.

1. Harmonising and simplifying adverse event reporting

- **A single EU Online Platform for Investigator-Sponsor/CRO Communication**

Investigators and data managers are responsible for reporting all participant health-related data to sponsors or CROs, including medical history, past and current medications, lab results, and adverse events. To fulfil this task, they currently face the challenge of navigating different Electronic Data Capture (EDC) systems across multiple clinical trials - depending on the sponsor or CRO managing each trial - or, in some cases, relying on paper-based systems. This lack of harmonization forces them to learn various platforms, manage multiple passwords, and sometimes resubmit reports due to issues such as illegible handwriting in paper records, leading to unnecessary follow-up queries and increased administrative burden.

We propose that the European Union introduce a single, integrated online platform that combines EDC functionality with a safety reporting system. This unified EU platform would enable investigators to enter participant data and adverse events (AEs), and to flag serious adverse events (SAEs) directly within the system for expedited SAE reporting to sponsors and CROs.

Additionally, the platform would act as a centralized communication hub, enabling investigators to receive periodic safety updates from sponsors or CROs. These updates could include individual Suspected Unexpected Serious Adverse Reactions (SUSARs) or periodic SUSAR line listings and Annual Safety Reports (ASRs). This would create a single, efficient communication channel for all safety-related reporting and interactions between investigators and sponsors/CROs.

Similar to the success of EudraVigilance, which has standardized safety reporting from sponsors/CROs to authorities, this integrated EU system would simplify and standardize reporting for investigators. The platform would use standardized templates and incorporate AI tools to ensure the use of consistent, widely accepted terminology, such as the ICH Medical Dictionary for Regulatory Activities (MedDRA). This is important, as the granularity of SAE descriptions currently leads to a situation where investigators (as well as National Competent Authorities and Ethics Committees) are overwhelmed with numerous, often redundant, individual safety reports. This approach would improve efficiency, ensure data consistency, and significantly reduce the administrative burden across clinical trials.

- **Simplification of Annual Safety Report (ASR) procedures for academic sponsors reporting to regulators**

The current CTIS system requires excessive detail for the ASR, placing an unnecessary burden on academic sponsors and Ethics Committees by generating additional, often irrelevant, workload. Furthermore, the lack of clarity in ASR requirements results in significant time spent by both parties handling numerous Requests for Information (RFIs).

To enhance the efficiency of this reporting process, the Coalition recommends that CTIS introduces a short and simplified template that expands automatically when high-grade adverse events are reported or optionally when sponsors need to provide additional details. Additionally, the reporting template should allow for cumulative updates, enabling sponsors to build upon previously submitted information rather than resubmitting unchanged data. It should contain obligatory use of the Common Terminology Criteria for Adverse Events (CTCAE) to improve fast discrimination between relevant and non-relevant information. The repetitive and long Development Safety Update Report (DSUR) templates still in use should be abandoned.

We believe that implementing clear and structured templates, including expandable icons with explanations and practical examples, would significantly reduce the need for RFIs and improve the overall efficiency of safety reporting.

2. Making use of the protocol to reduce excessive reporting from investigators to sponsors/CROs

Although the CTR allows sponsors to create protocols that reduce unnecessary safety reporting, investigators have not observed any noticeable changes since its implementation, likely as an unintended result of the significant flexibility that the CTR provides.

- **List of serious adverse events (SAEs) that do not need to be reported by investigators within 24h:**

Investigators are currently often required to report all serious adverse events (SAEs) within 24 hours during a clinical trial, even when they know the SAE is caused by the underlying disease and is not a SUSAR. This leads to unnecessary immediate reporting. To address this, we propose that sponsors adhere to the Clinical Trials Regulation, which allows for the exemption of certain SAEs from immediate reporting (Appendix 6). Anticipated events that are efficacy endpoints, consequences of the underlying disease, or common in the study population should be exempted from expedited reporting. To support this process, we suggest that sponsors submit a list of disease-related SAEs to the lead principal investigator for evaluation before the protocol is sent for regulatory assessment.

- **Grade 1 adverse events (AEs) that do not need to be reported by investigators**

Currently, investigators or delegated data managers are required to report non-serious adverse events twice: (i) in the hospital's Electronic Health Record (EHR) and (ii) in the sponsor's Electronic Data Capture (EDC) system. This process is inefficient, particularly for uninformative non-severe non-drug-related adverse events (e.g., grade 1 of Common Terminology Criteria for Adverse Events (CTCAE)) associated with the use of authorized drugs or drugs under investigation in phase III clinical trials. This duplication adds an unnecessary administrative burden, especially for events with little to no safety relevance.

To address this, we propose that sponsors include a comprehensive list of drug-related adverse events in the Investigator's Brochure (IB), categorized by organ and severity grade (using a standardized system like CTCAE and MedDRA). In line with the CTR (Appendix 7), sponsors should clearly state in the protocol that investigators in low-intervention and Phase III trials are only required to report Grade 1 adverse events that have been shown to be drug-related, and that are documented in the IB. This requirement should not apply to Phase III trials that follow a single-arm Phase II trial, where the absence of a control group limits the ability to reliably determine whether a Grade 1 adverse event is drug-related.

This recommendation would limit the reporting requirements to grade 1 adverse events with a reasonable causal relationship to the drug, reducing the administrative workload for investigators while maintaining relevant safety monitoring.

3. Following the CTR and guidelines to reduce excessive reporting from Sponsors/CROs to investigators

- **Frequency of SUSAR reporting from the sponsor/CRO to the investigator site**

To stay informed about potential emerging side-effects related to the study drug, investigators currently receive individual SUSAR reports and their follow-ups, which they must review and sign. This system, where individual SUSARs are sent rather than cumulative safety reports, often stems from sponsors adopting a one-size-fits-all strategy to satisfy the diverse requirements of health authorities in international trials. For example, while EMA provides flexibility by allowing either individual or cumulative reports, FDA mandates the submission of individual SUSARs. However, reports focused on isolated cases can be difficult to interpret in relation to the study drug, creating a heavy administrative burden that does little to enhance investigators' understanding of safety signals.

To address this issue, sponsors should follow the guidance outlined in the CTR Questions & Answers (Appendix 8), which advises informing investigators through periodic reports. Examples include periodic SUSAR line listings, which provide information on the

frequency and patients affected by SUSARs over a specific period, or ASRs, which according to ICH Guideline E2F, must include at minimum a list of all suspected serious adverse reactions (both expected and unexpected), an aggregate summary table of all reported serious adverse reactions organized by system organ class and study, and a comprehensive safety report. This report should contain a complete safety analysis and an evaluation of the benefit-risk balance of the investigational medicine, assessing its efficacy relative to its potential harm.

We recommend that European regulators also consider updating the CTR to require sponsors to provide such periodic safety profiles to investigators, especially during phase III and IV trials, instead of individual SUSARs. Sponsors should not be permitted to offload their administrative burden onto European investigators by applying the most conservative regulatory standards from one country of an international study to others with more flexible rules. By providing investigators with cumulative safety reports in the form of periodic SUSAR line listings and ASRs, which sponsors already submit annually to regulatory authorities, sponsors can ensure investigators remain informed while significantly reducing their administrative burden.

- **Restricting expedited reporting from sponsors/CROs to investigators to SUSARs only**

Some sponsors and CROs send individual reports to inform investigators about adverse events that are not classified as SUSARs. This may arise from the lack of clear guidance in the CTR regarding how sponsors should communicate safety information to investigators during clinical trials. Although both the Questions and Answers document accompanying the CTR and the ICH E6 (R3) Good Clinical Practice (GCP) guidelines - both of which sponsors and investigators are required to follow - touch on this matter, they do so in a rather general manner. Both sources state that sponsors should promptly notify all relevant investigators and institutions of findings that could impact participant safety and that they must expedite reporting of all SUSARs to them (Appendix 9). Such vague language risks encouraging sponsors and CROs to over-report any adverse event indiscriminately. The CTR should provide clearer directives on this issue, as investigators are currently inundated with a large volume of individual safety reports that offer minimal practical value. This influx can divert their attention from more critical data, potentially compromising participant safety.

To ensure investigators remain informed about adverse events not classified as SUSARs, without unnecessary overload, alternative approaches could include biannual line listings of severity-graded (CTCAE) adverse events. These listings would detail the frequency of each event per patient, the total number of affected patients, and the age distribution of those experiencing the events. Additionally, biannual or annual DSURs compiling all key safety information could provide a more streamlined and meaningful way to keep investigators updated while reducing administrative burden.

III. Informed Consent

The CTR explicitly states that the clinical trial information provided to participants should be comprehensive, concise, clear, relevant, and understandable to a layperson (Appendix 10). However, the requirement to inform participants of all aspects relevant to their decision-making (Appendix 11) often leads sponsors to adopt an overly cautious approach, resulting in excessively detailed Informed Consent Forms (ICFs). This tendency is especially pronounced in cases where exhaustive documentation is favoured by the Ethics Committees responsible for evaluating the ICFs.

This practice raises significant ethical concerns, particularly from an equitability point of view. The current state of informed consent creates barriers to participation in clinical trials for certain populations, leading to an unequal distribution of the risks and benefits of clinical research. We believe that the rules governing informed consent have become a substantial obstacle for many potential research participants, and we therefore recommend a comprehensive review of the consent process.

The Coalition believes that achieving fair, inclusive participation in clinical trials requires shorter, simpler, harmonised and patient-centered ICFs. To this end, we have revisited and refined our 2021 recommendations:

1. **Use of appendices for supplementary information:**

   Patient representatives identify the key sections of an ICF for decision-making as: study purpose, any prior use of the study medication in other treatments, screening tests, study procedures and treatments, alternative standard of care, key side effects, potential benefits, study duration, and contact information. Additionally, it is essential to state that participation is voluntary and that participants can withdraw at any time.

   Information beyond these essentials often reflects sponsors' requirements for regulatory compliance rather than patients' decision-making needs. This includes exhaustive details on data protection (such as the specific databases, coding methods, and storage locations for participant data) and descriptions of sample storage logistics. To streamline the ICF and improve clarity, we recommend moving this secondary information into an appendix, retaining in the main body only a layperson-friendly summary – prepared by someone with regulatory and legal expertise, and where appropriate in consultation with the organisation's Data Protection Officer – that includes all legally binding content. Additional non-critical details, such as less common side effects or thorough technical descriptions, may also be placed in these appendices. This way, participants receive a concise main document with only the information essential for informed decision-making, while the appendix remains available for those who wish to review further details.

2. **Focus on most-frequent side effects:**

   The side-effects section is often overwhelming for patients and not always clear. It is common practice to list numerous side-effects, many of them incomprehensible. We propose providing a shorter, more focused list of the most common side-effects, avoiding technical terms that are difficult for patients to understand (e.g., "Neutrophils: <1.5 x 10^3/µL"). Instead, we suggest using patient-friendly terms (e.g., "higher likelihood of infections").

3. **Use of visual aids:**

   To improve patient understanding, we recommend incorporating visual aids into screening and study procedures, as patients may not be familiar with specific tests. A clear, structured table with images could be an effective way to enhance comprehension. For example, in this format, the first column would display an image of each procedure, the second column would list the procedure's name, and the third column would offer a brief, optional description for further clarification. Additionally, a well-designed infographic summarizing the study design and treatment arms could complement a short-written description, providing patients with a quick, visual overview of the study flow and treatment options.

   Patients and patient representatives have frequently highlighted that videos explaining the clinical trial process significantly enhance understanding. Therefore, we strongly support the inclusion of videos in the informed consent process and recommend that CTIS be updated to enable their upload. While we acknowledge that this may require additional time for Ethics Committees to assess the informed consent forms, we believe their inclusion is beneficial for patient comprehension.

   This combined use of videos, images and concise explanations would facilitate clearer communication, ensuring that patients fully understand the study requirements.

To gain support for these recommendations – particularly from Ethics Committees, which hold decision-making authority regarding ICF acceptance – the Coalition has decided to gather feedback from patients on two alternative ICF versions based on our recommendations. One version (Appendix 12) aligns with the Council for International Organizations of Medical Sciences (CIOMS) guidelines, developed with the World Health Organization (WHO), recommending ICFs no longer than 2-3 pages. The second version (Appendix 13) is longer, to meet current regulatory requirements, but incorporates changes to enhance patient-centricity rather than focusing solely on legal terms.

The survey (Annex 2) revealed a strong preference by patients for either of the two ICF versions based on our recommendations over the original approved ICF (Annex 1). Respondents who favoured the version that deviates from the strict regulatory framework (Version 1, Appendix 12) highlighted its ease of understanding, visual appeal, and ability to provide comprehensive information in a concise format. However, many felt that it lacked certain details and suggested combining the two versions: the shorter Version 1 (Appendix 12) could serve as a 'visual

summary' or 'infographic overview', presenting key information in a brief, visually engaging way, while the longer Version 2 (Appendix 13) would offer additional context for those who require more detail. Almost all respondents agreed that the original ICF was overly detailed, technical, complex, and lengthy.

To support sponsors in adopting these changes within the regulatory framework, we propose developing a standardized ICF template based on this hybrid approach. Both the 'infographic overview' and the expanded ICF version would cover the primary elements of an ICF, which we believe should be harmonized across Europe and evaluated by Ethics Committees in a coordinated manner, similar to how National Competent Authorities currently assess Part I of clinical trial applications. While variations in standard of care between EU Member States may create challenges for harmonizing these key sections, strategies should be explored to address any discrepancies.

Additional, non-essential information – such as rare side-effects, the National Competent Authorities involved in trial approval and monitoring, and country-specific details like data protection or insurance policies – could be placed in appendices. This approach would allow each country's Ethics Committee to evaluate these supplementary sections independently, providing flexibility in meeting country-specific requirements while maintaining consistency across the main elements.

Finally, the ICF should be fully understandable on its own, as patients may be hesitant to ask questions out of concern it would inconvenience busy healthcare providers. However, it is essential that patients are informed of their right to ask questions and are provided with the contact information of a designated person responsible for addressing their concerns. The form itself is part of a broader consent process in which potential participants communicate with research staff, such as research nurses and the clinical team, allowing for questions and requests for clarification as patients decide about their participation.

REFLECTIONS ON THE IMPLEMENTATION OF THESE COALITION RECOMMENDATIONS

The Coalition for Reducing Bureaucracy in Clinical Trials wishes to emphasize that its aim is to 'reduce' bureaucracy, not – as tempting as it may sound to some – to eradicate it. Some administrative burden is simply inevitable and indeed necessary.

Most burdensome are administrative requirements that do not serve the quality and the effectiveness of clinical trials. The weaknesses in the CTR described in this document need to be corrected to ensure closer alignment of Europe's regulatory framework with the realities of clinical research. A regulatory framework that, despite its good intentions, is in some aspects disconnected from such realities can hinder medical progress in a high-tech region like Europe and limit access to innovative treatment options for patients.

The Coalition for Reducing Bureaucracy in Clinical Trials – with at its core Europe's major umbrella medical societies and patient advocates from across areas of disease – urges the European Medicines Regulatory Network (EMRN) to facilitate a comprehensive revision of the regulatory framework governing clinical trials in the EU. This should go hand in hand with revision of the MDR and IVDR to correct the current misalignment between the three regulations – a challenge addressed by the COMBINE project, which this Coalition fully supports. This process must involve key stakeholders from the outset, including clinical investigators (who design and conduct trials), patient advocates (representing trial participants), Ethics Committees (with multidisciplinary expertise in trial assessment), and commercial sponsors (which with the help of CROs facilitate and oversee the trials).

Many of the proposed improvements related to safety reporting and informed consent forms are already aligned with the current CTR and should be implemented without delay. The Coalition emphasizes the sponsor's responsibility to design studies that minimize unnecessary administrative burdens on investigators. Sponsors must ensure they have well-trained regulatory teams familiar with and adhering to the good clinical practice guidelines of the various countries involved in multinational trials. They should resist the temptation to simplify administrative work by applying the most conservative regulatory standards from one country to all participating countries. The best example is the requirement that sponsors report individual SUSARs in the US, as compared with EU regulators' encouragement to report aggregated SUSAR data. This practice creates excessive administrative burdens for investigators, ultimately compromising both patient safety and quality of care.

In this context, we acknowledge the intended benefits of the Common Protocol Template (CPT) developed by TransCelerate, which aims to standardize and streamline protocol development for sponsors. However, because CPT is designed for global applicability, it may prevent the targeted adjustments needed to alleviate the inefficient administrative burdens identified by this Coalition. We propose incorporating specific modifications based on our recommendations – already in alignment with the CTR – directly into the CPT. This would provide a rapid solution to ensure that sponsors conducting trials in the EU adapt protocols to European good clinical practice guidelines, fostering more efficient and investigator-friendly study designs.

At the same time, efforts toward international alignment should continue, allowing sponsors to adopt a single protocol template that meets all regulatory requirements while adhering to good clinical practice and maintaining efficiency across all participating countries.

Finally, we strongly encourage Ethics Committees to support the dissemination and uptake of EU-wide informed consent templates to promote patient centricity and standardization. Our survey has highlighted that a clear structure, the inclusion of infographics, and limiting document length are key for patients. Additionally, the template must explicitly mention that the main body of text should contain only a concise, lay-friendly summary, while the extended legal text is provided in an appendix.

The Coalition for Reducing Bureaucracy in Clinical Trials expresses gratitude to all investigators, patient advocates and others across Europe's clinical research ecosystem who have contributed to the development of these recommendations, and it calls on all stakeholders to apply them in designing, conducting, and regulating clinical trials.

Above all, the Coalition appeals to regulators, policymakers, sponsors, Ethics Committees and other stakeholders to collaborate to ensure that safety reporting requirements, informed consent practices, and the overall regulatory and ethics frameworks, do not harm what they are meant to protect: the quality of clinical trials and, above all, the safety of patients.

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Development of these recommendations:

These Coalition Recommendations are the result of years of collaborative work by investigators, patient advocates and regulatory experts whose organizations – medical societies, research organisations, patient advocacy networks – make up the Coalition for Reducing Bureaucracy in Clinical Trials.

An overview of Coalition members, endorsements, and collaborators can be found on the dedicated website: https://bureaucracyincts.eu.

Initiated and coordinated by the European Hematology Association (EHA) in close coordination with the BioMed Alliance, the Coalition first issued a joint statement in September 2020 titled 'Reducing bureaucracy in clinical trials: now is the time!'. In November 2021, the Coalition completed its first set of recommendations drafted by four thematic expert working groups, on (I) safety reporting, (II) informed consent, (III) regulatory guidelines, and (IV) harmonisation of requirements across the EU.

Expert groups on safety reporting, informed consent and 'regulatory' also laid the basis for this new, updated and expanded set of recommendations. Throughout the six years of Coalition building and recommendations development (2020-2025), the Coalition actively sought input from other stakeholders including policymakers, regulators, sponsors, and Ethics Committees, inter alia by organizing thematic roundtables and through dialogue with specific stakeholder groups.

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APPENDICES

I. Regulatory

Appendix 1. Streamlined and Aligned EU Clinical Trial Assessment Framework

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Recital 6**

The Member States concerned should cooperate in assessing a request for authorisation of a clinical trial. This co-operation should not include aspects of an intrinsically national nature, such as informed consent.

Appendix 2. Non-interventional trial definition

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Article 2. Definitions. Point 4.**

'Non-interventional study' means a clinical study other than a clinical trial;

***CTR Questions & answers*. Section 7. Safety Reporting**

1.7 Question: *What can be considered as a "non-interventional study"?*

17. Answer: Thus, a study is non-interventional if it does not fulfil any of the following conditions which define a Clinical Trial (according to Article 2 (2)(2) of the Clinical Trials Regulation:

a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;

b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or

c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Appendix 3. Low-intervention trial definition

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Article 2. Definitions. Point 3**

'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions:

(a) the investigational medicinal products, excluding placebos, are authorised;

(b) according to the protocol of the clinical trial,

(i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or

(ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and

(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;

Appendix 4. Requirements of paediatric clinical trials

The EU Clinical Trials Regulation No 536/2014 (CTR). **Article 32. Clinical trials on Minors. Point 1**

A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

(...)

(e) the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;

Appendix 5. Imperative of equitable inclusion of vulnerable populations in research

2024 revision of the Declaration of Helsinki. **Individual, Group, and Community Vulnerability. Point 19.**

Some individuals, groups, and communities are in a situation of more vulnerability as research participants due to factors that may be fixed or contextual and dynamic, and thus are at greater risk of being wronged or incurring harm. When such individuals, groups, and communities have distinctive health needs, their exclusion from medical research can potentially perpetuate or exacerbate their disparities. Therefore, the harms of exclusion must be considered and weighed against the harms of inclusion. In order to be fairly and responsibly included in research, they should receive specifically considered support and protections.

II. Safety reporting

Appendix 6. List of serious adverse events (SAEs) that do not need to be reported by investigators within 24h

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Annex I D. Protocol. Point 19**

With regard to the notification of adverse events, the protocol shall identify the categories of:

(a) adverse events or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor, and

(b) serious adverse events which do not require immediate reporting by the investigator to the sponsor.

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Annex I D. Protocol. Point 20**

The protocol shall describe the procedures for:

(a) eliciting and recording adverse events by the investigator, and the reporting of relevant adverse events by the investigator to the sponsor;

(b) reporting by the investigator to the sponsor of those serious adverse events which have been identified in the protocol as not requiring immediate reporting;

(c) reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database; and

(d) follow-up of subjects after adverse reactions including the type and duration of follow-up.

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Article 41. Point 2**

The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently.

The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.

Appendix 7. Grade 1 adverse events (AEs) that do not need to be reported by investigators

***CTR Questions & answers*. Section 7. Safety Reporting**

7.29 Question: *What adverse event reporting should be performed in low intervention trials?*

353.Answer: Safety recording and reporting in low intervention trials can be simplified from what is described in this document, applying a risk proportionate approach. Risk adaptations to safety

reporting refer to documenting of AEs in source documents, recording of AEs in the case report forms (and hence reporting to the sponsor) and to the requirements of immediate (not later than within 24 hours of obtaining knowledge of the event) reporting (of SAEs/SUSARs) by the investigator to the sponsor.

354.Answer: Any such adaptation should be clearly stated and justified in the protocol. Please refer to Chapter 4.2 in 'Risk proportionate approaches in clinical trials' (51).

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Annex I D. Protocol. Point 20**

The protocol shall describe the procedures for:

(a) eliciting and recording adverse events by the investigator, and the reporting of relevant adverse events by the investigator to the sponsor;

(b) reporting by the investigator to the sponsor of those serious adverse events which have been identified in the protocol as not requiring immediate reporting;

(c) reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database; and

(d) follow-up of subjects after adverse reactions including the type and duration of follow-up.

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Article 41. Point 2**

The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently.

The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.

Appendix 8. Frequency of SUSAR reporting from the sponsor/CRO to the investigator site

***CTR Questions & answers*. Section 7. Safety Reporting**

7.31 Question: *Should sponsors also send SUSARs to investigators of a clinical trial?*

357.Answer: The sponsor should promptly notify all concerned investigators/institutions of findings that could adversely affect the safety of the subjects and should expedite the reporting of all SUSARs to all concerned investigators/institutions (ICH E6) (52). The most important thing is to inform investigators of safety profile changes, not of individual SUSAR reports. For example, information derived from SUSAR reports could be provided via investigators' letters including both an updated benefit-risk evaluation and risk mitigation measures.

358.Answer: However, SUSAR reports contain unblinded data that usually should not be sent to investigators. The submission of individual safety reports to investigators may be justified if unblinded data is relevant for the management of the SAR. (…)

359.Answer: The safety information for investigators should be concise and practical. Whenever possible, the information on SUSARs should be at least a list of SUSARs that occurred at their MS, national territory, together with a summary analysis of safety profile and updated benefit risk for the ongoing clinical trials.

***European Medicines Agency Questions & answers*. Clinical Trials Information System (CTIS) and Clinical Trials Regulation (CTR), 9 February 2023**

Q41. Safety/SUSAR: Answer to Q7.30 in the EudraLex – Volume 10 Q&A on sending SUSARs to investigators of a clinical trial states, that the reporting of all SUSARS to all concerned investigators/institutions should be expedited. It also states that the most important thing is to inform investigators of safety profile changes, not of individual SUSAR reports. When is it required to report individual SUSARS to investigators? Does it apply to open or blinded SUSARS and SSRs?

Reporting of safety information to investigators is expected under the CTD/CTR. Overall, it is important that the investigators are informed about changes in safety profile, potential risks, and their mitigation. Therefore, individual SUSAR report is not to be provided as such to investigators. The information should be concise and practical. Therefore, the information on SUSARs should be aggregated in a line listing of SUSARs in periods as warranted by the nature of the research project/clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the IMP and an updated benefit risk.

Appendix 9. Expedited reporting from sponsors/CROs to investigators

***CTR Questions & answers*. Section 7. Safety Reporting**

7.31 Question: *Should sponsors also send SUSARs to investigators of a clinical trial?*

357.Answer: The sponsor should promptly notify all concerned investigators/institutions of findings that could adversely affect the safety of the subjects and should expedite the reporting of all SUSARs to all concerned investigators/institutions (ICH E6) (52). The most important thing is to inform investigators of safety profile changes, not of individual SUSAR reports. For example, information derived from SUSAR reports could be provided via investigators' letters including both an updated benefit-risk evaluation and risk mitigation measures.

***The EU Clinical Trials Regulation No 536/2014 (CTR)*. Article 47**

The sponsor of a clinical trial and the investigator shall ensure that the clinical trial is conducted in accordance with the protocol and with the principles of good clinical practice.

***GCP ICH E6 (R2).* Section 5.16. Safety Information**

5.16.2. The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

***GCP ICH E6 (R2).* Section 5.17. Adverse drug reaction reporting**

5.17.1. The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

***GCP ICH E6 (R3).* Section 3.13.2. Safety Reporting**

> (b) The sponsor should, in accordance with the applicable regulatory requirement(s) and with ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, expedite the reporting to the regulatory authority(ies) of all adverse drug reactions (ADRs) that meet three criteria: suspected, unexpected and serious (i.e., SUSARs).
>
> (d) The reporting of SUSARs to investigator(s)/institutions(s) and to the IRB(s)/IEC(s) should be undertaken in a manner that reflects the urgency of action required and should take into consideration the evolving knowledge of the safety profile of the product. Reporting of SUSARs to the investigators/institutions should be made in accordance with regulatory requirements. In some regions, periodic reporting of line listings with an overall safety assessment may be appropriate.
>
> (e) Urgent safety issues requiring immediate attention or action should be reported to the IRB/IEC and/or regulatory authority(ies) and investigators without undue delay and as specified in regulatory requirements.

III. Informed Consent

Appendix 10. The information in the ICF shall be comprehensive, concise, clear, relevant, and understandable to a layperson

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Article 29. Informed consent. Point 2**

Information given to the subject or, where the subject is not able to give informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall:

(a) enable the subject or his or her legally designated representative to understand:

(i) the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;

(ii) the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification;

(iii) the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; and

(iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued;

(b) be kept comprehensive, concise, clear, relevant, and understandable to a layperson;

Appendix 11. The ICF should include all aspects of the clinical trial relevant to the subject's decision to participate

***The EU Clinical Trials Regulation No 536/2014 (CTR).* Article 2. Definitions. Point 21**

'Informed consent' means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial;

IV. Informed Consent Form Templates

Appendix 12. Infographic

(see following pages)

Ibrutinib in treatment of mantle cell lymphoma

Your participation in this clinical trial is entirely **voluntary**. If during the study you decide that you want to withdraw, you may do so without giving any reason. Just let your doctor know.

Aim of the study

Improve the treatment outcomes for patients with mantle cell lymphomas using a treatment called Ibrutinib.

Has this treatment been used before?

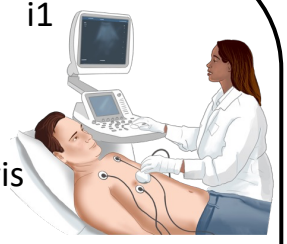
Ibrutinib is currently approved by the European Medicines Agency (EMA) for use in patients with chronic lymphocytic leukaemia and Waldenstrom disease (two other types of lymphoma). For the treatment of mantle cell lymphoma, it is approved for patients who have previously received at least one previous therapy to treat their lymphoma. It has not been approved for the initial treatment of your disease.

Test to evaluate if you can participate in the study

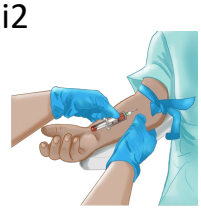
The following test are part of the routine Standard Of Care (SOC):

1. Electrocardiogram and ultrasound of the heart
2. Collection of around 50mL of blood
3. Bone marrow puncture
4. Computer tomography (CT) of neck, chest area, stomach and pelvis
5. A biopsy of your tumour

i1



i2



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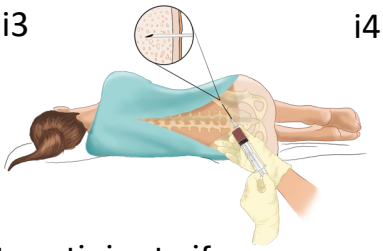
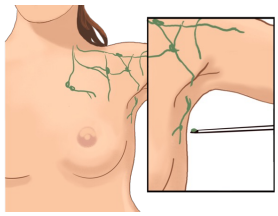


i4

i5



You cannot participate if you are pregnant or breastfeeding. You should use contraception during the study and probably sometime afterwards. Your doctor will evaluate your participation in case you are taking additional medication

Brief description of the study

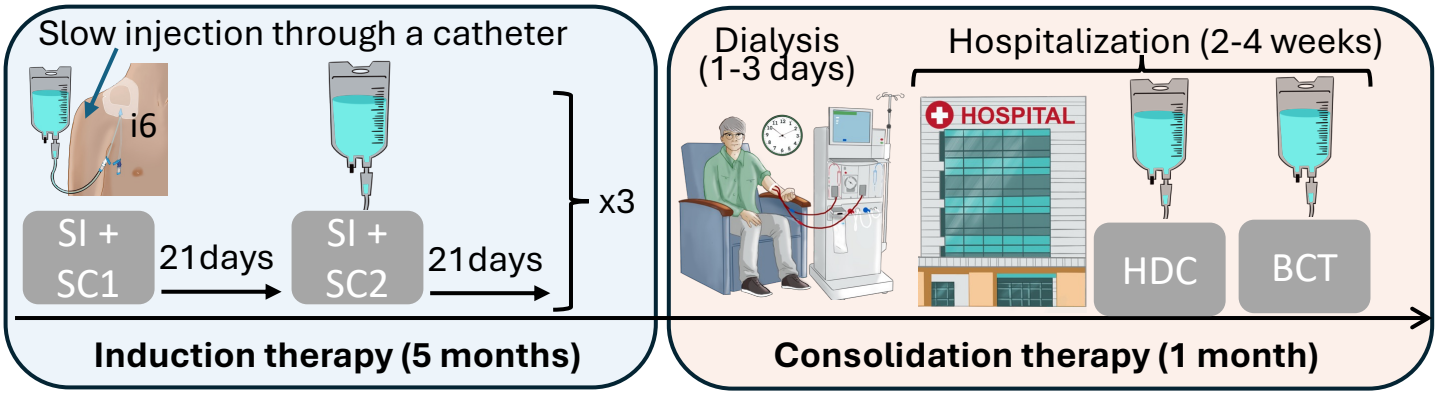
In this clinical trial three different treatment regimens are being compared. Treatment 1 consist on the current standard therapy (induction and consolidation therapy). Treatment 2 consist on the current standard therapy but with Ibrutinib pills added during the induction therapy and a maintenance period. Treatment 3 also adds Ibrutinib pills during the induction therapy, but replaces the consolidation therapy by the maintenance period, which also includes Ibrutinib. Patients are randomly (as if by the roll of dice) assigned to the treatments to get equal numbers of patients in each treatment for their scientific comparison

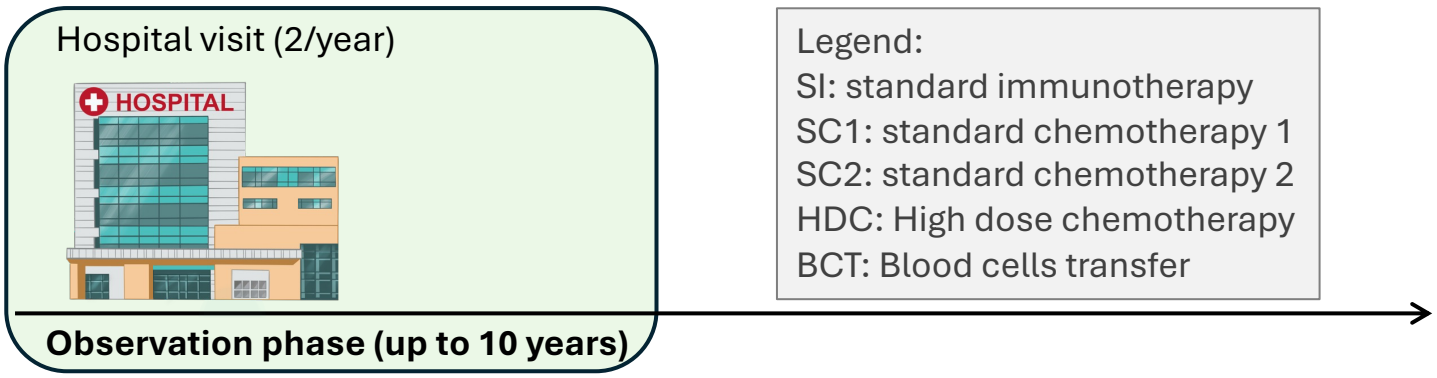
Standard of care & Investigational treatment (randomly assigned)

Invasive tests performed during the 3 treatment options:

- Blood collection (i2) 15mL (SOC) or 30mL (study)
- Computerised tomography (i4) every 6 months (SOC)
- Tissue sample biopsy (i5) optional (SOC)
- Bone marrow puncture (i3) optional every 6 months (SOC)
- Central venous catheter placement in neck or below collarbone (i6) (SOC)

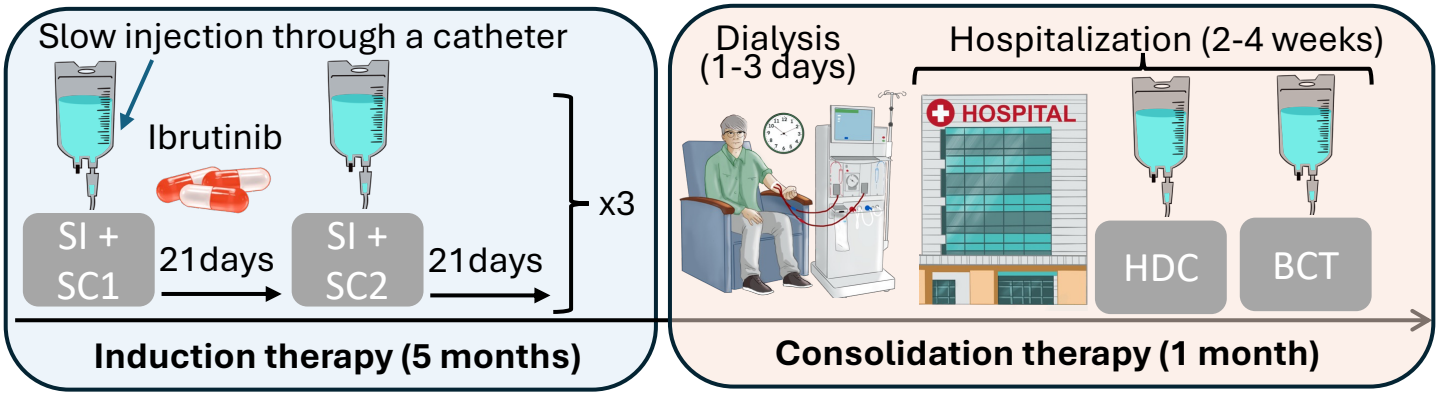
Treatment 1 (standard of care = SOC):

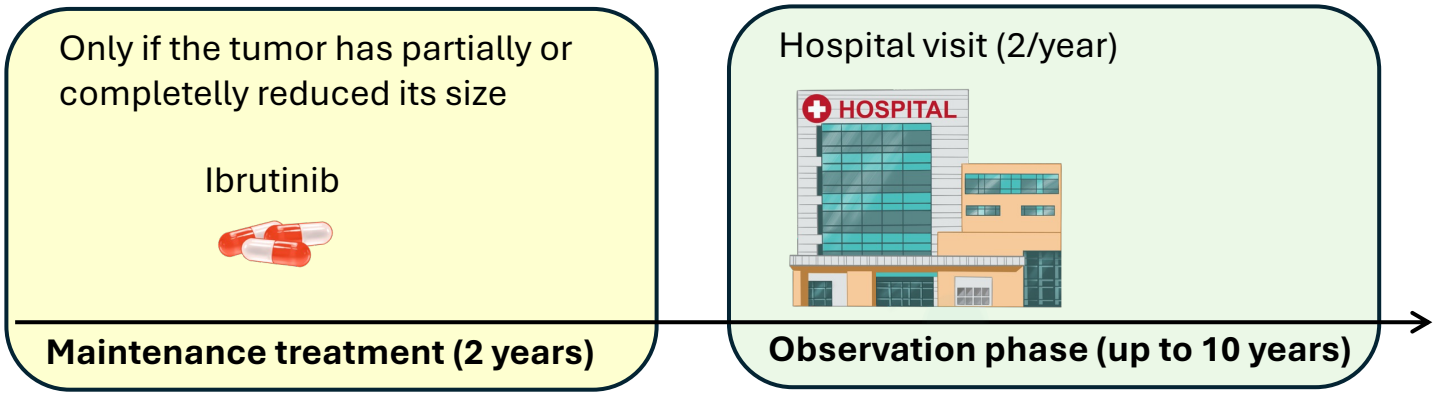




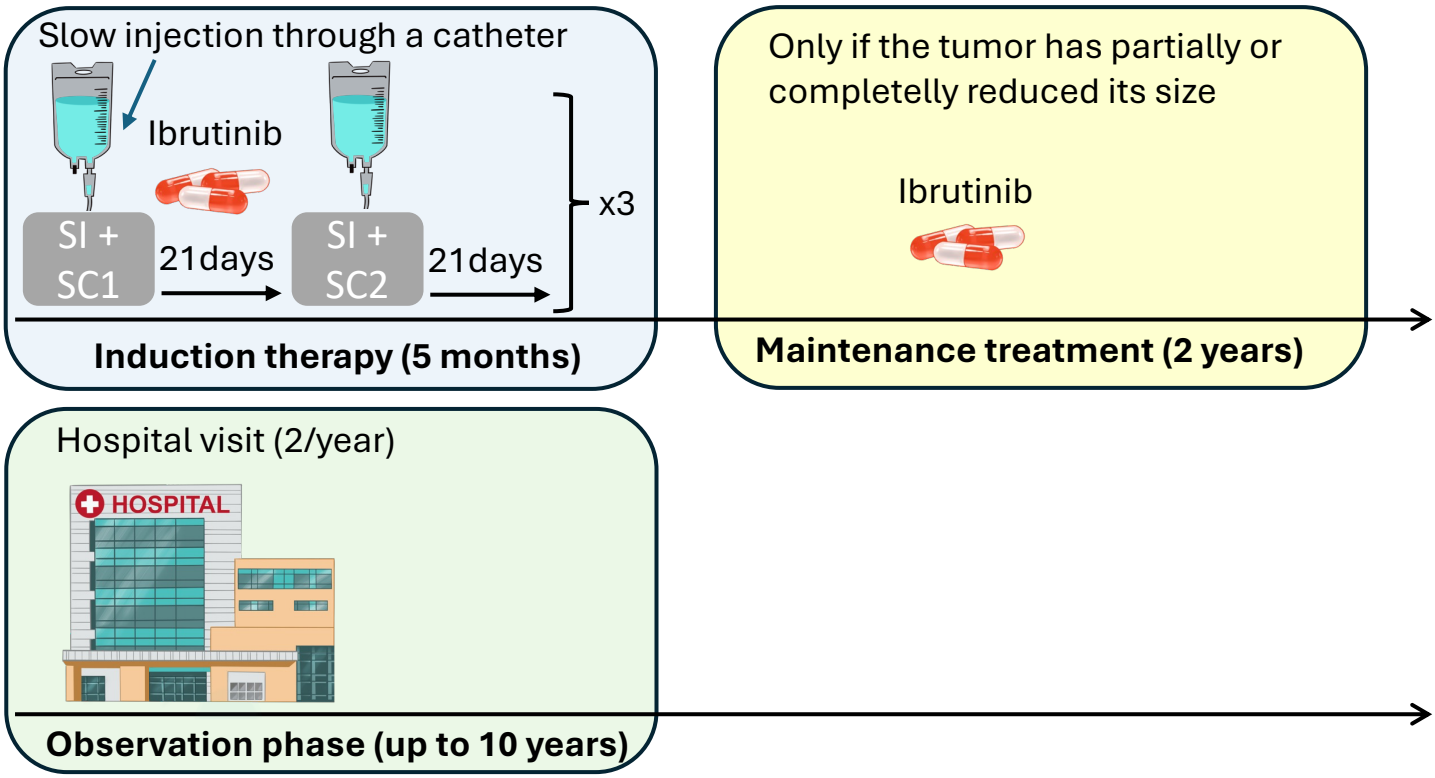
Legend:
SI: standard immunotherapy
SC1: standard chemotherapy 1
SC2: standard chemotherapy 2
HDC: High dose chemotherapy
BCT: Blood cells transfer

Treatment 2:





Treatment 3:



You can exit the study if you do not follow your doctor's instructions or if your doctor considers that you would benefit more from another treatment.

Your **identity** will be **fully protected,** even if you consent to donnate data/samples to research. Anonymous trial data may be made public.

Risks (1 out of 5 patients):

-Loose or watery stool (diarrhoea)
-Muscle and joint pains
-More infections due to neutropenia
-Wound clotting difficulties and bruises due to thrombocytopenia
-More respiratory infections (colds)
-Bleeding (Haemorrhage) Rash
-Nausea
-Fever

Risks (1 out of 10 patients):

-Shores in mouth
-Constipation
-Swelling hands or feet
-Vomiting
-Skin infection
-Inflammation of the lungs
-Headaches
-Muscle cramps
-High blood pressure
-Dizziness
-Urinary tract infection
- Weakness, tingling, numbness, and pain from nerve damage, usually in the hands and feet

Reasonable benefits:

Option B or C may or may not produce a better regression of the lymphoma than Option A (or standard care), but several studies have shown that Ibrutinib can lead to the regression of mantle cell lymphomas

Contact:

Study nurse:
Hospital:

Use the **study nr: XXXX** to access the results of the study once they will be made available here: link CTIS web

Appendix 13. Short ICF

(see following pages)

Key information section

Name of the study

TRIANGLE study on the use of ibrutinib for the treatment of mantle cell lymphoma.

Purpose/aims of the research study

The aim of this study is to improve outcomes for patients with mantle cell lymphoma using a treatment called ibrutinib. Ibrutinib is a treatment currently used for other lymphomas, but not mantle cell lymphoma.

What does involvement in this study involve?

We would like to invite you to take part in this study.

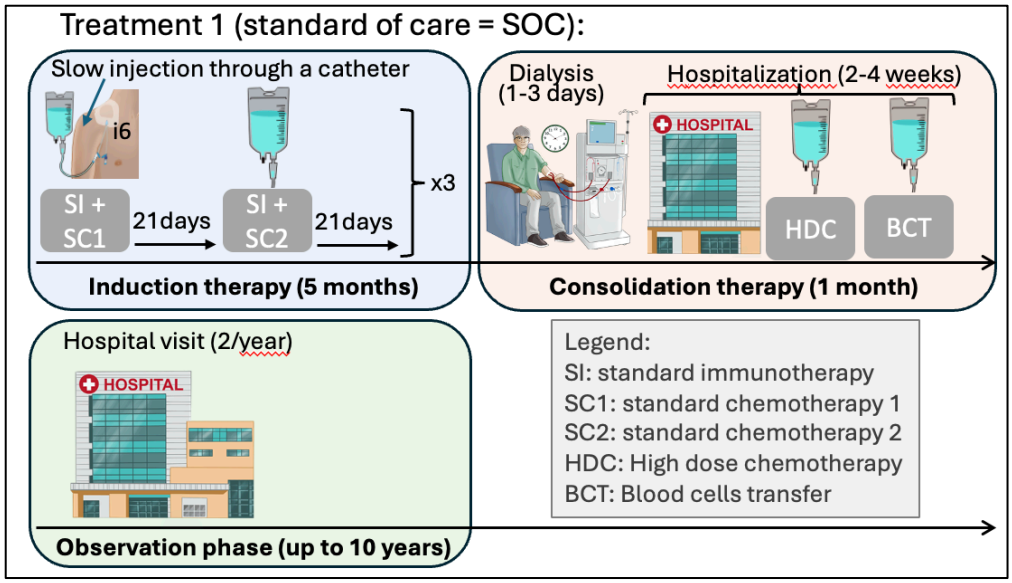
Before entering the study, your medical history will be collected, and you will have a detailed medical examination to make sure there are no medical reasons to stop you entering this study.

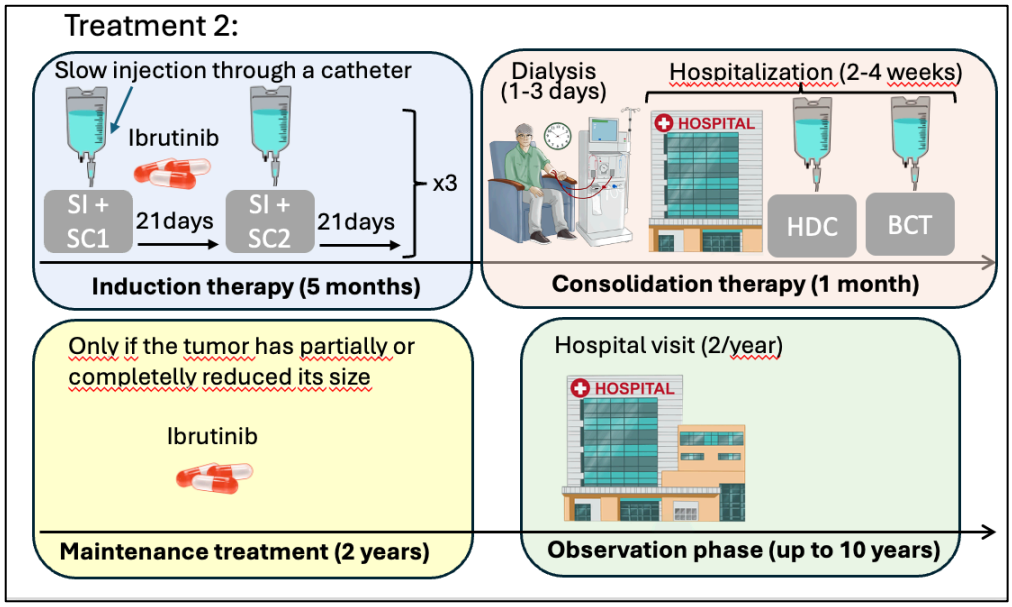
When taking part in this study, you will visit your study centre over a period of up to 10 years.

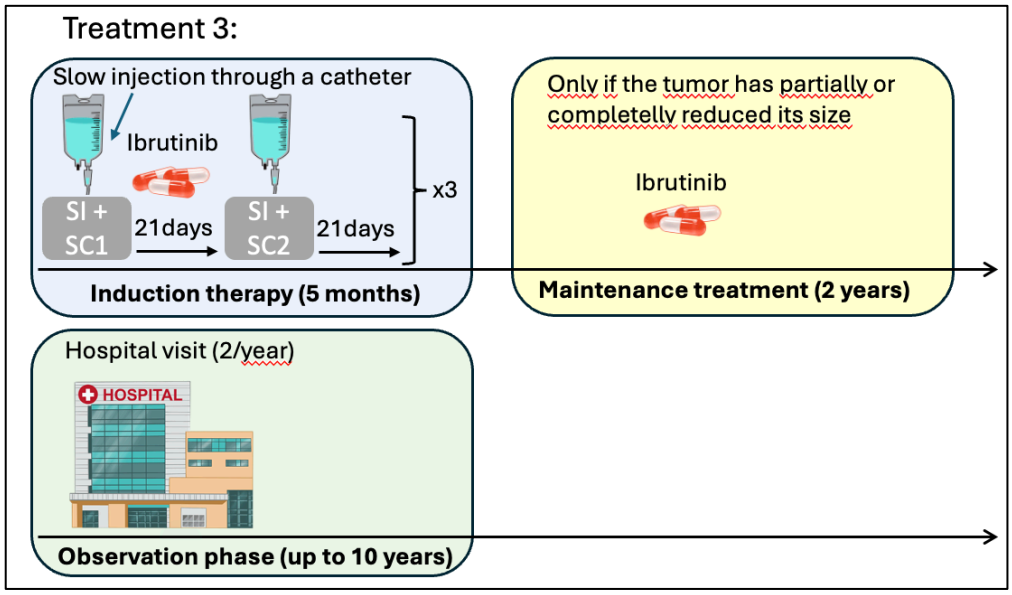
You will be randomly put into a one of three treatment groups. This allows us to compare different treatments:

1. If you are allocated to treatment Arm A you will be treated with the current standard therapy (immunotherapy and chemotherapy). This consists of an 'induction' phase of alternating chemotherapy and immunotherapy. The induction phase lasts about 5 months. This is followed by a 'consolidation' phase using a higher dose of chemotherapy and infusion of some of your own blood cells (an autologous stem cell transplant). This phase lasts about one month, and you could be in hospital for 2-4 weeks. Finally, there is an 'observation' phase or follow-up for at least 5 years with visits to the study centre at least twice a year.
2. If you are allocated to treatment Arm A+I you will be treated with current standard therapy (immunotherapy and chemotherapy) plus ibrutinib. Ibrutinib will be given during the 'induction' phase and the 'consolidation' phase of treatment. This will be followed by a 'maintenance' phase, where you will be treated with ibrutinib for up to 2 years to try to stop your lymphoma from coming back. During this time, you will need to visit the study centre every 3 months. This will be followed by the 'observation' phase.
3. If you are allocated to treatment Arm I you will be treated with current standard therapy (immunotherapy and chemotherapy) plus ibrutinib. This will be followed by the 'maintenance' phase, where you will be treated with ibrutinib for up to 2 years to try to stop your lymphoma from coming back. During this time, you will need to visit the study centre every 3 months. This will be followed by the 'observation' phase.

The diagrams below explain the treatment pathway for the different treatment groups.


Treatment 1 (standard of care = SOC):
Slow injection through a catheter
i6
SI + SC1
21days
SI + SC2
21days
x3
Induction therapy (5 months)
Dialysis (1-3 days)
Hospitalization (2-4 weeks)
HOSPITAL
HDC
BCT
Consolidation therapy (1 month)
Hospital visit (2/year)
HOSPITAL
Observation phase (up to 10 years)
Legend:
SI: standard immunotherapy
SC1: standard chemotherapy 1
SC2: standard chemotherapy 2
HDC: High dose chemotherapy
BCT: Blood cells transfer


Treatment 2:
Slow injection through a catheter
Ibrutinib
SI + SC1
21days
SI + SC2
21days
x3
Induction therapy (5 months)
Dialysis (1-3 days)
Hospitalization (2-4 weeks)
HOSPITAL
HDC
BCT
Consolidation therapy (1 month)
Only if the tumor has partially or completelly reduced its size
Ibrutinib
Maintenance treatment (2 years)
Hospital visit (2/year)
HOSPITAL
Observation phase (up to 10 years)


Treatment 3:
Slow injection through a catheter
Ibrutinib
SI + SC1
21days
SI + SC2
21days
x3
Induction therapy (5 months)
Only if the tumor has partially or completelly reduced its size
Ibrutinib
Maintenance treatment (2 years)
Hospital visit (2/year)
HOSPITAL
Observation phase (up to 10 years)

Do I have to be involved in this study?
No. Your participation in this study is completely voluntary. You will be involved in this study only after you have given your consent in writing. If you decide that you do not wish to take part in this study or decide to withdraw from it at a later stage, you may do so without giving any reason. Your future care and treatment will not be affected.

What are the risks of being involved in this study?
You may have side effects from the medications or procedures used in this study; these side effects may differ from person to person. There are side effects associated with the current standard of care (immunotherapy and chemotherapy) and there are also side effects reported by patients who have received ibrutinib in other studies for different forms of lymphoma. It is important to note that there are some risks associated with the treatment. The most common side effects are listed below, and the less common side effects are summarised in Appendix 1.2.

All patients in the study are carefully monitored for side effects. There may be some side effects that the study doctors and sponsor are not aware of yet. Side effects may have different severities from mild to very severe. It is possible that your health may worsen during this study. Your doctors can, however, manage most side effects. Many side effects disappear quickly if their causes are treated. In some cases, side effects can be serious, last a long time and/or be permanent. There is also a slight risk of death from the treatment. This is why you should inform your doctor immediately of any changes that affect your health and that you notice while taking part in the study.

Below are highly common side effects experienced by at least 1 in 5 patients treated with ibrutinib:

- Increased frequency of loose or watery stools (diarrhoea)
- Muscle and joint pains (musculoskeletal pains)
- Low white blood cell count (cells that help fight infection) (neutropenia)
- Low platelet count (thrombocytopenia, affects blood clotting)
- Common cold (upper respiratory tract infection)
- Bleeding (haemorrhage)
- Rash
- Nausea
- Fever (pyrexia)

Listed below are highly common side effects experienced by 1 in 10 patients:

- Sores in mouth (stomatitis)
- Constipation (obstipation)
- Swelling of hands or feet (peripheral oedema)
- Joint aches (arthralgia)
- Vomiting
- Skin infection
- Inflammation of the lungs (pneumonia)
- Headaches
- Muscle cramps (muscle spasms)
- High blood pressure (hypertension)
- Weakness, tingling, numbness, and pain from nerve damage, usually in the hands and feet (peripheral neuropathy)
- Dizziness
- Urinary tract infection

A list of the less common side effects can be found in Appendix 1.2.

What may be the benefits of taking part in this study?
You suffer from a rare form of lymphoma, and standard therapy is not satisfactory. If you receive ibrutinib, there is a possibility that there will be an improvement in your treatment and that better regression of the lymphoma can be achieved. However, the effectiveness of the combination of ibrutinib and standard treatment (immunotherapy and chemotherapy) is not yet known. It may be possible that you will not get any benefit from taking part in this clinical study.

The information gained from this study will increase the knowledge of how ibrutinib can be used for the treatment of patients with mantle cell lymphoma. This information may also possibly help other people with your disease in the future.

Who can I contact if I have further questions or want more information?

Function	Name	Contact information
Study Doctor	XXX	+XXXXXXXXXX
Study Nurse	XXX	XXXXX

What is the study treatment and what is the standard therapy?
Standard therapy for mantle cell lymphoma consists of an 'induction' phase, when the immunotherapy, rituximab, is given in combination with chemotherapy. The chemotherapy is alternated every 3 weeks between CHOP (cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine (Oncovin®) and prednisone) and DHAP (cytarabine (Ara-C), cisplatin and dexamethasone). The induction phase lasts 5 months, which is 3 cycles of each immunotherapy plus chemotherapy combination.

After the 'induction' phase, standard therapy continues with the 'consolidation' phase. This is when a much higher dose of chemotherapy is given. This higher dose of chemotherapy is harmful to healthy cells, and particularly to the cells in the bone marrow (blood stem cells). To be able to give high dose chemotherapy safely, it is necessary to collect blood stem cells from the blood before the start of treatment and to freeze and store them to use later. Blood stem cells are immature cells. Mature blood cells are formed from blood stem cells in the bone marrow. They can be collected from the blood using a process called haemodialysis. They are returned to the patient after thawing by infusion into a vein in the arm. The cells find their own way to the bone marrow, grow there and form new mature blood cells within 10 to 14 days. This way the tumour cells can be exposed to very high doses of chemotherapy without the risk of permanent damage to the blood stem cells in the bone marrow. This process is called autologous stem cell transplantation.

Patients in two of the study treatment Arms (A and A+I) will receive standard of care with the induction and consolidation phases. Patient in study treatment Arm I do not have a consolidation phase.

Ibrutinib blocks a protein on lymphoma cells, which effects how these cells grow and survive. By blocking this protein, ibrutinib can kill lymphoma cells. Several studies have already shown that ibrutinib can lead to the regression of mantle cell lymphomas. In this study, ibrutinib will be given in combination with the immunotherapy and chemotherapy in two of the treatment Arms (A+I and I). Patients in both these treatment Arms will have a 'maintenance' phase. This will come after the 'consolidation' phase for treatment Arm A+I or after the 'induction' phase for treatment Arm I. During the 'maintenance' phase patients will take daily tablets of ibrutinib for up to 2 years.

Ibrutinib is currently approved by the European Medicines Agency (EMA) and by the German authorities for use in patients with chronic lymphocytic leukaemia and Waldenstrom disease (two

other types of lymphoma). It is approved for patients with mantle cell lymphoma who have been previously treated for their lymphoma. It has not been approved as a first treatment for mantle cell lymphoma (see Appendix 1.1 for more information).

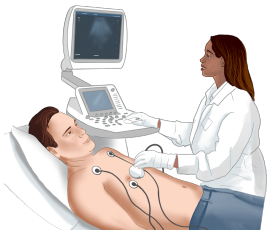
What additional examinations and/or interventions are needed for the study?

Tests before entering the study

The following tests or procedures must be done to find out whether you may be included in the study. These tests and procedures will be carried out according to routine clinical practice. If some tests or procedures have been done recently, then it is possible that you may not have to redo them. Your doctor will decide whether they need repeating. The following must be carried out before the start of study treatment:

- ECG and ultrasound of the heart (1)
- CT scan of neck, chest area, stomach and pelvis (2)
- Bone marrow puncture to investigate lymphoma in the bone marrow (3)
- Blood tests for pregnancy (women of child-bearing potential only), HIV, hepatitis B and C, and lymphoma cells (4)
- Blood tests for kidney disease, liver disease and blood cell count (4)
- A sample of tumour tissue will be taken and sent to a laboratory to confirm your diagnosis (5)

1



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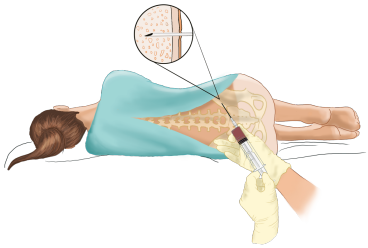

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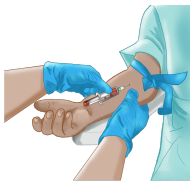

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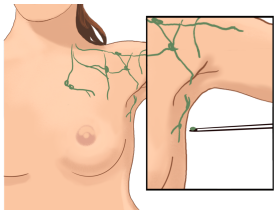

Your ability to take part in this study depends on the results of these tests. If the tests show that you are suitable for the study, and you decide to take part, you will be invited to come back to the study centre to receive treatment.

Tests during the study

The following tests or investigations will be done during the study. They can be done multiple times throughout your time in the study. All these tests or investigations are part of your routine medical care and are usually needed even if you do not take part in the study. Your study doctor will explain the tests or investigations to you:

- Medical examination, including height, weight, blood pressure and pulse (several times during and after the infusions)
- Assessment of your everyday activities, performance and general health
- Blood tests for kidney function, liver function and blood cell count
- CT scan of your neck, chest area, stomach and pelvis to see if you have had a response to the treatment (about every 6 months)

- A sample of tumour tissue may be taken and sent to a laboratory to see if your lymphoma has progressed (optional)
- You will be fitted with a central venous catheter. This is a plastic tube that is inserted in a large blood vessel in the neck or below the collarbone
- A bone marrow puncture is essential to assess the spread of the disease. This procedure is usually performed under local anaesthesia and should be done twice a year. This procedure is optional but is more accurate than blood samples to assess the spread of the disease.

In addition to the standard tests listed above you will need to give a blood sample approximately every 3 months during the first year and twice a year for the following 4.5 years. The blood sample will be used to measure the number of lymphoma cells in your blood.

Can I withdraw from the study?
If you decide that you no longer want to take part in the study, you must tell your study doctor immediately. Your doctor will let you know about other possible treatments and will perform a final assessment, if needed (and with your consent). You should also discuss what happens to your personal data after you withdraw from the study (see Appendix 2.1, 2.2 and 2.3). You do not have to give a reason for withdrawing from the study. Your future treatment will not be affected if you withdraw from the study.

How will my personal data be stored and kept confidential?
During the study, your study team will collect and record in writing all medical findings and personal information about your general health, your response to treatment, side effects and other health issues, and test results in your personal file at the study site. This personal data will be saved electronically. The information that is essential to the study will be saved under a code from which you cannot be identified to ensure that your personal data remains confidential.

The data is protected against unauthorised access. Decoding will occur only under the conditions prescribed by law.

More details on how we use and store your data is available in Appendix 2.2

Who can I ask questions about the study?
Contact information for the study team:

Name	Position	Telephone	Email	Availability	Contact with:
Dr. X	Principal Investigator (doctor)				
Dr. X	Investigator (doctor)	+XXXXXXXXXXX	Urgent.doctor@hos.com	24/7	Urgent side effects
Y	Nurse	+XXXXXXXXXXX	CT.nurse@hos.com	Weekdays 9am-18pm	General study questions
	Study pharmacist?				

Patient Consent Form

Study Code: ..... Site ID Code: ..... Participant identification number: .....

Study title: This could be the same as in the protocol or a simplified patient-friendly version

Name of Researcher: ..... If you agree, please initial or tick box

1. I confirm that I have read the information sheet dated..... (version.....) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the Sponsor, from regulatory authorities and from the national health service, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. (If appropriate) I agree to provide a sample(s) as part of my involvement in this study and I understand I will not gain any direct personal or financial benefit from them.	
5. (If appropriate) I agree to audio/video recording and the use of anonymised quotes in research reports and publications.	
6. (If appropriate) I agree to my General Practitioner being informed of my participation in the study.	
7. (If appropriate) I understand that the information held and maintained by the Sponsor or other central healthcare bodies may be used to help contact me or provide information about my health status.	
8. (Genetic research, if appropriate,) I understand and agree that my samples will be used in research aimed at understanding the genetic influences on disease and that the results of these investigations are unlikely to have any implications for me personally.	
9. (MRI studies, if appropriate): I understand that this is a research scan that is not useful for medical diagnosis, and that scans are not routinely looked at by a doctor. If a concern is raised about a possible abnormality on my scan, I will only be informed if a doctor thinks it is medically important such that the finding has clear implications for my current or future health.	
10. I agree to take part in this study.	
11. (If appropriate) I agree to be contacted about ethically approved studies for which I may be suitable. I understand that agreeing to be contacted does not oblige me to participate in any further studies.	
12. (If appropriate) I agree for my anonymised samples to be used in future research, here or abroad, which has ethics approval.	

Name of participant.....Date.....Signature.....

Name of person taking consent.....Date.....Signature.....

Appendix 1

Appendix 1.1 – Study approvals

Fill in the following squares and write if the principal investigator and/or other members of the hospital are being paid for their role in the study and if there are any conflicts of interest
Contact information of those conducting the clinical trial:

Name	Position	Telephone	Email	Availability	Contact with:
Dr. X	Principal Investigator (doctor)				
Dr. X	Investigator (doctor)	+XXXXXXXXXX	Urgent.doctor@hos.com	24/7	Urgent side effects
Y	Nurse	+XXXXXXXXXX	CT.nurse@hos.com	Weekdays 9am-18pm	General study questions
	Study pharmacist?				
	CRA?				

The study has been approved by the following regulatory authority:

- European Medicines Agency (EMA)

The study has been approved by the following research ethics committees:

- National research ethics committee (if applicable)
- Local hospital research ethics committee

The study is organised by (sponsor and/or CRO):

- The name of the sponsor/CRO/research hospital/clinic

The principal investigator and the study nurse are paid for conducting the study. There are no conflicts of interest.

Appendix 1.2 – Less common side effects to Ibrutinib

It may be that you experience some unwanted side effects or symptoms while taking part in this study with Ibrutinib. You should inform your doctor of any side effects that you experience.

The side effects listed below have been reported by patients who have been treated with Ibrutinib in clinical trials and in hospital.

The following side effects have been reported by more than 1 of every 100 patients:

- Increased levels of a substance called uric acid in the blood (hyperuricemia)
- Abnormal heart rhythm (atrial fibrillation)

- Non-melanoma skin cancer
- Increase in specific white blood cell counts (leucocytosis, lymphocytosis)
- Blurred vision
- Low white blood cell counts with fever (febrile neutropenia)
- Redness of the skin (erythema)
- Breaking of the nails (onycholysis)
- Inflammation within the lungs that may lead to permanent damage (interstitial lung disease)
- Severe infection throughout the body (sepsis)
- Sinus infection (sinusitis)
- Increased level of a substance called creatinine in the blood

The following side effects have been reported by less than 1 of every 100 patients:

- Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat or seizures (tumour lysis syndrome)
- Itchy rash (urticaria)
- Inflammation of the fatty tissue underneath the skin (panniculitis)
- Swollen face, lip, mouth, tongue or throat (angioedema)
- High white blood cell counts with abnormal clumping that can lead to bleeding (leucocytosis syndrome)
- Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)
- Tender or painful bumps or ulcers on the skin, sometimes with a fever (neutrophilic dermatoses)
- Liver failure
- Abnormal rapid and irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (ventricular tachyarrhythmias)
- Temporary or permanent decrease of brain or nerve function due to reduced blood flow to the brain (mini-stroke or stroke).

Most of these side effects were mild to moderate. However severe side effects have been reported. Some side effects have been severe enough for the patient to stop taking Ibrutinib, change the dose, be hospitalised, cause disability and very rarely, death.

You should inform your study doctor or study team of any side effects that you notice. Your study doctor will be able to manage your side effects with medication, if needed, or prevent them from getting worse. Your study doctor may eventually decide to stop treatment with Ibrutinib for a short time or to lower the dose until all side effects are gone.

Appendix 1.3 – Contraception and pregnancy during the study

Pregnant women should not take part in this study. All women of childbearing potential must take a pregnancy test at the start of the study. This test must be negative to be able to participate. Postmenopausal women do not need a pregnancy test.

If you take part in this study and you could become pregnant, you must agree to use two reliable contraception methods at the same time. These must be considered by your study doctor as

being highly reliable (less than 1% failure rate per year). They must be used for the entire treatment duration and for at least 12 months after the last administration of Rituximab, or at least 3 months after the last administration of Ibrutinib, whichever is the longest.

Reliable means of contraception are a combination of the following:

- Intrauterine device (IUD), birth control pill using two hormones, contraceptive implants or 3-monthly injections, sterilisation of male partner (e.g., vasectomy) **together with one of the following barrier methods:**
- Latex condoms by the male partner, diaphragms and contraceptive caps.

If sexually abstaining (defined as abstaining from all types of sexual activities), you need no further contraception methods.

Note: some birth control pills may not work if you are taking certain medications, suffer from vomiting or have diarrhoea. Should you have any questions, please talk to your study doctor. If you are taking birth control pills and suffer from vomiting or diarrhoea, please inform your doctor as the methods of contraception may have to be changed in such cases.

The reason for these precautions is that it is not yet clear whether Ibrutinib can be harmful to unborn children if this medication is taken during pregnancy. You may, therefore, expose yourself and your child to some unknown risks. No one knows what those risks are. It is known however that certain medications can cause women to give birth to children too early or that the children may exhibit birth defects.

Because pregnancy remains possible even when responsibly using a reliable method of contraception, you must agree to inform your study doctor as soon as possible during the study if your method of contraception has failed or if you are pregnant. Your study doctor or study team will explain any potential risks for your unborn child and will explain which options are available to you. Because of the potential risks for your baby, the trial medication will be stopped immediately. Even if you become pregnant within 12 months after taking the trial medication for the last time, you must immediately inform your investigator. In case of pregnancy, you will be asked whether you agree to inform your doctor of the outcome of the pregnancy, and that the information relating to any potential effect from Ibrutinib on the child may be collected.

Breastfeeding mothers should not take part in this study either, since the immunochemotherapy or Ibrutinib may get into the breast milk and thus into the child's body, and lead to potential damage.

Fertile males who have not been sterilised must use an effective method of contraception to avoid conceiving a baby. These must be considered by your study doctor as being effective (e.g., condoms or diaphragm). They must be used for the entire treatment duration and for at least 12 months after the last administration of Rituximab, or at least 3 months after the last administration of Ibrutinib, whichever is the longest.

Furthermore, you must consent to ask your female partner to use an additional method of contraception such as oral contraceptives, IUD, a barrier method or a spermicide. You must accept the risk that pregnancy remains possible even when responsibly using a reliable method of contraception. You must agree to inform your study doctor as soon as possible if your method of contraception has failed or your partner is pregnant. Your study doctor or study team will explain any potential risks for your unborn child and will explain which options are available to you and your partner. If your partner becomes pregnant, you and your partner will be asked

whether you agree to inform your study doctor of the outcome of the pregnancy, and that the information relating to any potential effect from Ibrutinib on the child may be collected.

You should not make any sperm donations while you are receiving immunochemotherapy or Ibrutinib, and for another 12 months after taking Rituximab for the last time or 3 months after taking Ibrutinib for the last, whichever is the longest.

Appendix 1.4 – Additional study information

Ibrutinib is a drug that is still being investigated in clinical trials. Ibrutinib blocks a protein in lymphoma cells to stop the cells from growing and to kill the lymphoma cells. Several studies have already shown that Ibrutinib can lead to the regression of mantle cell lymphomas.

Appendix 2 – Data, samples and patient protection

Appendix 2.1 – Monitoring of personal data during the study

Before starting the study, the safety and execution of the study are reviewed in accordance with strict ethical guidelines by an independent ethics committee. The ethics committee will monitor this study until it has finished. They will review the side effects reported during the study to ensure the safety of the patients taking part in the study. The ethics committee could decide to pause or stop the study if the severity and number of side effects is greater than expected and they decide it is not safe for patients to continue in the study.

Appendix 2.2 – Personal data

How will my personal data be stored and kept confidential?

During the study, your study team will be collecting personal information, information about your general health, and medical findings for the study in your personal health file. They will also collect information about your response to study treatments, side effects, other health issues, and the results of the tests done during the study. This personal data will be collected and saved on paper and stored electronically at the study site for analysis.

The personal data that is collected for the study will be anonymised and saved under a patient code. This is done to make sure that your personal data remains confidential. All your personal data will be protected against unauthorised access.

Who will be using the data collected during this study?

Your anonymised data will only be used by the people who are given the authority to do so under this declaration of consent for research purposes in direct connection with lymphomas and similar diseases. These people can be in Germany, in other European countries, in the USA and other countries, such as Canada, South and Central America, Japan, China, Australia and Southeast Asia. Some countries outside Europe may not have the same data protection regulations as Germany. The sponsor will treat all personal information collected as confidential within the limits of the law.

The results can be used in reports about the study or for scientific lectures or publications. In these cases, you will not be mentioned by name, and you will not be identified.

What are the laws that protect my identity during the study?

You will be required to give voluntary written informed consent for the collection and processing of your personal data. The laws for the collection, processing and protection of personal data are governed by the EU-General Data Protection Regulation (GDPR), revised German Federal Data Protection Act (BDSG-neu) and the Guidelines for Good Clinical Practice. In addition, the European Regulation on Clinical Trials with Medicinal Products for Human Use (No. 536/2014) and the German Medicines Act (AMG) also apply.

What are my rights under data protection law?

You have the right access your own personal data that is collected during the study. You have the right to have a copy of this data free of charge (Art. 15 GDPR, §§ 34 BDSG-neu). Under

certain circumstances, you have the right to have your personal data deleted (Art. 17 and 19 GDPR, §§ 34 BDSG-neu). Under certain conditions, you have the right to request a restriction on the processing of your data, i.e. the data may only be stored but not processed. To exercise these rights, you must contact your study doctor or the data protection officer (Art. 18 and 19 GDPR).

You have the right to request the correction of inaccurate personal data. (Art. 16 and 19 GDPR). If you decide to withdraw from the study, no further data will be collected. The sponsor can, however, keep and continue to use the data that has already been collected as part of the study. The sponsor must do this to fulfil its legal obligations and maintain the scientific integrity of the study. You may request that the samples that were collected from you are destroyed if you can be identified from them.

Will my family doctor/hospital team have access to my personal data?

By giving your written consent, you agree that your family doctor and/or hospital team be informed of your participation in this study.

During the study, your family doctor/hospital team will be able to contact the study doctors to discuss your condition. To help prevent any confusion, it will be necessary to check your personal data (i.e. clinical data with name, first name and date of birth). For this to happen, you will need to release your study doctor from maintaining medical confidentiality.

What happens to my personal data?

Your data will be anonymised for analysis. Analysis of the study data will be done using patient codes, which consist of a combination of letters and numbers. It will be impossible to refer to you by name and very difficult to identify you.

If the results from the study are published in scientific journals, only anonymised data will be used. Data protection laws apply to publications, and it will be impossible for you to be identified.

You have the right to lodge a complaint with the supervisory authority(ies) if you believe that the processing of personal data concerning you is not lawful (Art. 77 GDPR).

You can either visit the supervisory authority responsible for you or contact the person responsible for data processing at your trial site or you can contact the sponsor about this.

You can either visit the supervisory authority responsible for you on the website of the Federal Representative for Data Protection and Freedom of Information at:

https://www.dataprotectionwebsite.com

or contact the data responsible for data processing at your trial site or you can contact the sponsor about this.

The sponsor of the clinical trial is responsible for data processing. The person responsible for this task is:

Name / Function:	Dr XXXXXX / Head of the Research Clinic
Address:	XXXX Research Clinic Street Town/City

Postcode/Zip code
Country

Tel: +XXXXXXXXXXX
E-Mail: studycentre@hos.com

*If the Head of Research Clinic changes the successor is responsible for data processing.

Appendix 2.3 – Samples and biopsies

What happens to my tissue samples, blood samples and bone marrow samples?

Tissue samples will be sent to a doctor who studies cells and tissues under a microscope (a pathologist) and a central laboratory. There the tissue samples will be assessed to confirm your diagnosis. Your tissue samples will be stored and made available to further lymphoma research studies.

The blood samples and/or bone marrow samples will be anonymised and sent to a central laboratory for storage. These samples will be made available to further lymphoma research studies.

The release of tissue and/or blood samples for other lymphoma research studies needs to have approval from an ethics committee before any investigations are started.

Your consent to the use of tissue and/or blood samples for further research studies will be obtained separately. If you do not give your consent, the tissue and/or blood samples will be destroyed once the study is over. You can participate in this study, even if you have not given your consent concerning the use of tissue and/or blood samples for research studies.

Appendix 2.4 – Are there any costs to me for taking part in the study? Do I receive compensation?

There are no additional costs to you when taking part in this study. All tests and examinations needed for this study that would not usually occur as part of your routine care are free of charge for you. However, you or your health insurance must cover the costs associated with medications and services provided at a hospital, practice, clinic or doctor's office that are part of your normal medical care.

Your participation in this study is not compensated.

Appendix 2.5 – Am I insured during the study?

All patient taking part in this study are insured in accordance with the Medicines Act. The insurance cover extends to the General Conditions of Insurance for all health conditions that may occur as a result from you taking part in the study and for a period of up 5 years after you leave the study. In accordance with the General Conditions of Insurance, the maximum sum insured is EUR 500,000 per person. It only addresses a financial disadvantage; it does not pay compensation for damages.

If you suspect that your health has been damaged or your existing medical condition has worsened due to your participation in the study, you should immediately and directly inform the insurance company, with the support of your study doctor, as appropriate, to avoid jeopardising your insurance cover:

Name of insurance company
Address
Tel.: +XXXXXXXXXXX
Email: enquiries@insuranceco.com
Insurance number/ Police No.: XXXXXXXXX

If your study doctor supports you in this, obtain a copy of the report. If you are contacting the insurance company directly, make sure to also inform your study doctor. You can make this notification in person or by phone. When explaining the cause or the scope of damage, you must cooperate and do everything possible to avert and reduce damage. If you have suffered damage as a result from your participation in this study, you will receive appropriate medical treatment. Your doctor will explain which options are available to you and tell where you can be treated.

For the duration of the clinical trial, you should undertake another medical treatment only after you have consulted your study doctor, except in cases of emergency. You must immediately inform the study team of any emergency treatment you have undergone.

You may request a copy of the Conditions of Insurance. We would like to draw your attention to Item 1.4 (on exclusions), Item 3.1 (on scope of services) and Items 4.3 and 4.4. (on your obligations).

We would also like to point out that you are not insured against accidents on the way to and from the study centre.

Appendix 2.6 – Will I be informed of new findings during the study?

You will be informed of any new findings from this study and told immediately of any findings that could influence your willingness to continue to take part in the study. In this case, you can reconsider your decision to continue in the study. When you become aware of such findings and you agree to continue to take part in the study, you will need to sign an updated informed consent form.