Stellungnahme der ISD zum Kommissionsentwurf eines European Biotech Act I

Allgemeiner Teil

Mit dem im Dezember 2025 veröffentlichten Entwurf der Europäischen Kommission eines European Biotech Act I kann nach unserer Einschätzung zukünftig auch die klinische Forschung in der Europäischen Union von dringend notwendigen frischen Stimuli in beträchtlichem Umfang profitieren. Die EU-Kommission lässt mit ihren Vorschlägen ein neues Zielbewusstsein für die Bedeutung klinischer Prüfungen in der Union erkennen, das vor dem Hintergrund des Wissens um die Schwächen der EU-Verordnungen über klinische Prüfungen mit Humanarzneimitteln (CTR) als auch der über Medizinprodukte (MDR) bei der Initiative Studienstandort Deutschland (ISD) grundsätzlich Anerkennung findet.

Die im Rahmen des Biotech Act 1 angestrebten Änderungen sind unter Berücksichtigung der von den zeichnenden Verbänden und Akteuren gemachten Anpassungen sehr zügig rechtlich und – im Falle von CTIS organisatorisch – zu implementieren. Perspektivisch sollte in einem weiteren Verfahren eine grundlegende Reform der CTR angestrebt werden. In dieser Hinsicht verweisen wir auch auf das 12 Punkte-Papier des MedEthicsEU-Vorstands (Anlage 1).

Nichtsdestotrotz sieht die ISD in den Zielen des Entwurfs des EU-Biotech Act einen wichtigen Ansatz zur Stärkung des Studienstandortes Europa insgesamt. Die Verkürzung von Genehmigungsfristen, eine stärkere Harmonisierung zwischen den Mitgliedstaaten und eine Vereinheitlichung von datenschutzrechtlichen Regelungen sind dringend notwendig und werden endlich (und fast schon zu spät) mit der nun gestarteten Befassung der EU-Kommission durch die Umsetzung des bereits von Draghi angemahnten regulatorischen Reformstaus auf EU-Ebene adressiert. Eine zügige Umsetzung des Biotech Act I in geltendes Recht und ein funktionales CTIS-Portal sind daher dringend geboten.

Spezieller Teil

Unbedingt notwendig und unverzichtbar sind die Änderungen der CTR, die darauf abzielen, die Zeiten für bestimmte Prozesse in der Bearbeitung der Anträge auf Genehmigung der Durchführung klinischer Prüfungen zu verkürzen. Das betrifft insbesondere den Vorschlag, die Bearbeitungsfristen für multinationale klinische Prüfungen von im Sinne der CTR max. 106 Tagen auf max. 75 Tage bzw. 47 Tage zu reduzieren, sollte kein RFI notwendig sein. Davon ebenso betroffen ist die Verkürzung des Bearbeitungsprozesses von Anträgen auf die Genehmigung wesentlicher Änderungen. Des Weiteren möchten wir die Wichtigkeit der Reduzierung der Validierungsfrist auf max. 7 Tage und das Abschmelzen der max. Gesamtbewertungsdauer

multinationaler klinischer Prüfungen auf max. 42 Tage unterstreichen. Das umfasst auch die Anpassung der max. Reaktionszeit für den Sponsor auf 14 Tage sowie den Wegfall der zusätzlich möglichen max. 50 Tage Bewertungsdauer für ATMP. Behördliche Bewertungsprozesse werden zukünftig dadurch gestrafft und dortige ineffiziente Leerlaufzeiten vermieden. Wir möchten das BMG auffordern, sich für eine Priorisierung und unveränderte Umsetzung dieser Maßnahmen einzusetzen. Diese Terminverkürzungen werden jedoch nur erfolgreich sein, wenn das CTIS Portal grundsätzlich besser funktioniert. Andernfalls befürchten wir eher eine Verschlechterung der Situation.

Aus Sicht der ISD ist auch die Stärkung der Führungsrolle des RMS im Sinne des vorgeschlagenen Artikels 4 Abs. 2 Satz 2 in der CTR ein richtiger Schritt. Auch der Fakt, dass zukünftig in multinationalen klinischen Prüfungen die Bewertung des RMS bei Teil 1 des Bewertungsberichts die maßgebliche Referenz für die betroffenen Mitgliedstaaten sein wird, halten wir für einen guten Schritt in die richtige Richtung. In diesem Sinne wird die verpflichtende Einbeziehung der Ethik-Kommission des RMS in die Bewertung von Teil I des Bewertungsberichts gemäß Artikel 4 Abs. 3 S. 2 und Art. 6 Abs. 2 Unterabs. 2 CTR begrüßt. Gemäß Erwägungsgrund 130 sieht die ISD darin einen Weg zu einer lang eingeforderten einheitlicheren, harmonisierten ethischen Bewertung.

Die Neufassung der koordinierten Bewertung der betroffenen Mitgliedstaaten durch eine verkürzte Mitwirkung dieser Staaten und Beschränkung ihrer von ihnen vortragbaren Bedenken auf die in Artikel. 8 Abs. 2 Unterabs. 2 in der CTR genannten Gründe sowie ethischer Versagungsgründe im Sinne des neuen Artikels 6 Abs. 5 Unterabs. 3 in der CTR halten wir für konsequent.

Eine stringente Validierung von Teil 1 des Bewertungsberichts durch den RMS gemäß Art. 5b CTR wird begrüßt. Im Zuge der Validierung erfolgt auch die Prüfung, ob die klinische Prüfung in den Anwendungsbereich der VO (EU) 536/2014 fällt oder ob ein „low-intervention“ oder „minimal-intervention clinical trial“ vorliegt. Eine entsprechende Überprüfung erfordert klinische und pharmakologische Fachkenntnisse und gehört zu den zentralen Aufgaben der zuständigen Ethik-Kommission. Vor diesem Hintergrund sollte analog zur obligatorischen Einbeziehung der Ethik-Kommission des RMS bei der Bewertung von Teil 1 des Bewertungsberichts auch im Hinblick auf die Validierung von Teil 1 des Bewertungsberichts sichergestellt werden, dass die zuständige Ethik-Kommission des RMS einbezogen wird. Dafür sind ausreichende Fristen erforderlich.

Positiv ist auch, dass die parallele Einreichung wesentlicher Änderungen grundsätzlich ermöglicht werden soll. Nach dem Entwurf wäre dies aber nur für wesentliche Änderungen zulässig, die bestimmte, voneinander unabhängige Aspekte des Dossiers betreffen. Dadurch könnten Studien schneller angepasst und das Studienmanagement für Sponsoren vereinfacht werden. Aus Sicht der ISD sehen wir darüber hinaus den Bedarf, dass auch innerhalb einer Studie parallele Einreichung wesentlicher Änderungen möglich wird – ggf. risikoadaptiert.

Überprüft werden sollte dagegen nochmals das Alignment zwischen Teil I und Teil II der Bewertung. Es ist von grundlegender Bedeutung, dass die aktuell bestehenden Probleme bei der zeitlichen Abstimmung zwischen den Bewertungen des Teils I und Teils II ausgeräumt werden und nicht mehr zu zeitlichen oder inhaltlichen Verzögerungen und Unsicherheiten beitragen. Das wäre im Sinne aller Beteiligten – Behörden, Ethikkommissionen und Antragsteller. Es sollte daher darüber nachgedacht werden, einen zusätzlichen Artikel 6a in die Verordnung einzuführen, der die zeitliche Kohärenz zwischen der inhaltlichen Bewertung der beiden Teile explizit sicherstellt und eine klare zeitliche Abstimmung vorsieht.

Begrüßenswert ist dagegen die Einführung eines harmonisierten Kern-Antragsdossiers im Sinne der neuen Artikel 27a bis Art. 27c, Abs. 2 Nr. 38 CTR (neu)), um klinische Prüfungen mit demselben Prüfpräparat zu vereinfachen als auch die Einführung von Reallaboren im Sinne des Artikels 2 Abs. 2 Nr. 45 in der CTR.

Erfreut betrachten wir die Einführung eines beschleunigten Genehmigungsverfahrens für klinische Prüfungen in medizinischen Notlagen als auch eines Verfahrens zur Bewertung von Anträgen von kombinierten klinischen Prüfungen im Sinn des Artikels 14 c.

Die Erleichterungen für „low-intervention“ und „minimal-intervention“ clincial trials werden begrüßt. In den Erwägungsgründen werden insbesondere für nicht-kommerzielle Sponsoren deutliche Vereinfachungen damit verknüpft. In den vorgeschlagenen Gesetzesänderungen selbst sind die Änderungen im Hinblick auf Erleichterungen bei der Antragstellung nicht so ausgeprägt, wie die Erwägungsgründe erwarten lassen. Vor allem für die „low-intervention clinical trials“ sind mehr Erleichterungen analog zu den Regelungen für „minimal-intervention clincial trials“ für die Stärkung der Studien der Akademia anzustreben. Die neue Kategorie der „minimal-intervention“ trials bezieht sich ausschließlich auf zugelassene Substanzen innerhalb der zugelassenen Indikation (OECD A, Anlage 2), aber leider nicht auf zugelassene Substanzen außerhalb der zugelassenen Indikation, aber mit unterstützenden wissenschaftlichen Daten (OECD B1). Wir fordern, die „minimal-intervention“ clinical trials auf die OECD B1 Gruppe klinischer Prüfungen auszudehnen. Die Zuteilung der Studien zu „minimal-“ und „low-intervention clinical trials“ sollte gemeinsam durch die Bundesoberbehörden und die Ethikkommission getroffen werden, bei der Definition der „normalen klinischen Praxis“ müssen die europäischen oder nationalen Medizinischen Fachgesellschaften wesentlich einbezogen werden, die Bewertung eines „minimal additional risk“ muss durch die Ethikkommission vorgenommen werden.

Die Erleichterungen in der Antragstellung und im Safety-Reporting bei „minimal-“ und „low-intervention clinical trials“ sollten zudem konkret definiert und beschrieben werden. Erleichterungen, die nur nach Ermessen erteilt werden, bieten keine Planungssicherheit. Wir schlagen hier als Leitfaden die „Danish Medicines Agency’s guidance on risk-based recording and reporting of adverse events in clinical trials on medicinal products under Regulation (EU) no. 536/2014“ vor (Anlage 3).

Das gilt auch für die geplanten Adaptierungen der CTR an die Datenschutzgrundverordnung und mit den einhergehenden Erleichterungen im Datenschutz im Sinne des Artikels 93 Abs. 7 in der CTR und die Ansätze in den Erwägungsgründen 150 bis 153. Die Rechtsgrundlagen für die Verarbeitung personenbezogener Daten im Rahmen von klinischen Prüfungen soll Art. 6 Abs. 1 lit. c) und Art. 9 Abs. 2 lit. i) (und j) DS-GVO sein. Eine Abweichung im nationalen Recht (wie das Einwilligungserfordernis im AMG) soll damit ausgeschlossen werden (neuer Art. 93 Nr. 7/8). Die Weiterverarbeitung von Daten durch den gleichen Verantwortlichen soll im Rahmen von anderen klinischen Prüfungen oder zu bestimmten wissenschaftlichen Forschungszwecken zulässig sein. Dies ist zu begrüßen.

Zudem sieht der Ansatz vor, dass Sponsor und Prüfzentrum datenschutzrechtlich Verantwortliche sein sollen – das folgt der bekannten Auslegung in Deutschland. Die Zusammenarbeit zwischen Sponsor und Prüfzentrum ist datenschutzrechtlich regelmäßig als gemeinsame Verantwortlichkeit nach Art. 26 DSGVO einzustufen, da die ärztliche Tätigkeit, die Erhebung der Daten und die Betreuung der Studienteilnehmenden eigenverantwortlich durch den Prüfarzt erfolgen und nicht den Weisungen des Sponsors unterliegen. Ein Auftragsverarbeitungsverhältnis nach Art. 28 DSGVO würde die Freiheit der medizinischen Forschung, die berufsrechtlichen Pflichten der Ärzte (u. a. nach Deklaration von Helsinki) und die persönliche Verantwortung des Prüfarztes für Einwilligung und Datenschutz unzulässig einschränken. Aktuell sehen wir hier eine große Heterogenität in der Auslegung dieser Frage auf Ebene der Mitgliedstaaten und dieser Ansatz im Entwurf des EU Biotech Act würde den „Wildwuchs“ in der Auslegung dieser Frage endlich europäisch einheitlich regeln.
Damit würden sich hoffentlich die langjährigen Auslegungsfragen und Unsicherheiten für die Anwender reduzieren und wir sollten eine bessere Einheitlichkeit in der EU sehen. Wir sehen daher in den Ansätzen gerade auch für den Studienstandort Deutschland – aber auch für die EU insgesamt – wichtige Verbesserungen.

Kritisch sehen wir hingegen die angedachte Änderung im neuem Artikel 93 Abs. 8 in der CTR, wonach zukünftig für sämtliche Verarbeitungstätigkeiten geeignete technische und organisatorische Maßnahmen getroffen werden müssen, was nach unserer Einschätzung einen erheblichen bürokratischen Mehraufwand bedeutet.

Besonders kritisch sehen wir, dass das CTIS im Biotech Act nicht die Beachtung findet, die dringend notwendig ist. Mit dem Wissen um die zahlreichen Mängel und Unzulänglichkeiten des Systems hätte ein eigenes Kapitel mit den dafür notwendigen Reformvorschlägen integriert werden müssen. Dies gilt es noch dringend im Gesetzgebungsverfahren zu adressieren. CTIS ist das zentrale System, über das der gesamte Prozess läuft. Daher ist es weder für die Antragsteller noch die nationalen Behörden und Ethikkommissionen hinnehmbar, dass dieses System weder nutzerfreundlich noch gut handhabbar ist. Hier zu grundlegenden Verbesserungen zu kommen, ist ebenso entscheidend für die Zukunft des Studienstandortes Europa wie die bereits adressierten Änderungen. Zur Weiterentwicklung von CTIS gehört dabei auch die Implementierung von Schnittstellen für den tagesaktuellen Export der Daten zur Verwendung in anderen Portalen. Vor diesem Hintergrund wird gefordert, im Vorfeld der vorgesehenen

Aufstellung des Entwicklungsplans gemäß Art. 98a CTR eine Evaluation unter Einbeziehung der unterschiedlichen Nutzergruppen durchzuführen.

Insgesamt kommt es aus unserer Sicht beim EU Biotech Act darauf an, die Chancen zu heben, Europa wieder zu einem starken Wettbewerber im internationalen Vergleich der Studienstandorte weltweit werden zu lassen. Mit diesem Gesetzgebungsverfahren müssen daher alle relevanten Hebel in Bewegung gesetzt werden, um die Weichen für die Zukunft zu stellen.

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Initiative Studienstandort Deutschland (ISD)

Die **ISD** hat sich im November 2023 aufgesetzt und diskutiert Verbesserungsmöglichkeiten im Hinblick auf die Durchführung klinischer Prüfungen am Studienstandort Deutschland. Insgesamt ist das Ziel der ISD, den Studienstandort Deutschland in allen Ebenen wieder attraktiver zu machen und somit mehr Studien an den Standort Deutschland zu holen. Die Initiative Studienstandort Deutschland (ISD) besteht derzeit aus über 20 Organisationen aus dem Umfeld der Klinischen Forschung sowie beratenden Gästen.

Zu den Mitgliedern gehören:

- Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland e.V. (AKEK),
- Bundesverband der Pharmazeutischen Industrie (BPI),
- Bundesärztekammer (BÄK),
- Bundesverband des nicht-ärztlichen Studienpersonals in der klinischen Forschung e.V. (BUVEBA),
- Bundesverband Medizinischer Auftragsinstitute e.V. (BVMA),
- Bundesverband Medizintechnologie e.V. (BVMed),
- Deutsche Hochschulmedizin e.V. (DHM),

Deutsche Gesellschaft für Hämatologie und Med. Onkologie e.V. (DGHO),

Deutsche Gesellschaft für Pharmazeutische Medizin e.V. (DGPharMed),

Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V.,

Netzwerk der Koordinierungszentren für Klinische Studien (KKS-Netzwerk),

Leibniz Gemeinschaft,

Pharma Deutschland e.V.,

Verband der Diagnostica Industrie e.V. (VDGH),

Verband Forschender Arzneimittelhersteller e.V. (vfa).

Daneben sind weitere Organisationen beratend an den Diskussionen beteiligt:

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF),

Initiative Deutscher Forschungspraxennetze (DEGAM-ForNet)

Deutsche Forschungsgemeinschaft (DFG),

Netzwerk Universitätsmedizin (NUM),

Sachverständigenrat Gesundheit & Pflege (SVR),

Wissenschaftsrat (WR).

Proposals to initiate discussion for Revision of the CTR within the European Biotech Act

Disclaimer: This proposal is the view of the MedEthicsEU board and consultation with relevant stakeholder is essential as next step.

Preamble
The EU Clinical Trials Regulation (CTR) contains valuable principles but requires urgent revision to make Europe attractive again for clinical research (commercial and non-commercial) and to prevent further "international drift" of trials to regions with less rigorous focus on patient protection and data quality. Accelerating approval timelines alone without structural revisions will not solve the systemic problems in the current process and may undermine the essential role of Medical Research Ethics Committees (MRECs). We therefore propose the following priority changes:

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1. Introduce risk-proportionate, flexible procedures and reduce administrative burden
The CTR's "one size fits all" approach applies almost identical requirements to low-risk, post-approval studies (e.g. treatment optimization) and to high-risk trials with novel investigational products. A revised CTR must introduce clearly defined risk categories (e.g., DKMA Denmark[1], OECD recommendations on governance clinical trials[2]) and proportional procedures for approval and surveillance in one specific chapter. The administrative burden should also not equally apply to all risk categories of clinical trials.
For national and multinational **risk categories 1 and 2** (see DKMA Denmark or OECD risk category A and B1) trials, the full CT authorisation process should be simplified and replaced a MREC authorisation only.

Risk category 3 (or OECD category 2B and C) clinical trials should be assessed by NCAs and MRECs . For these trials, MREC should be consulted not only for assessment part 2, but mandatory also for part 1 of a CTA (DoH 2024[3] and ICH E6 GCP R3 2025[4]).

A **risk-proportionate safety reporting system** (see also CTCG addendum to safety reporting[5]) should be implemented in the CTR 536/2014 and/or Commission Implementing Regulation (EU) 2022/20 concentrating on aggregated instead of individual reports (lean obligatory templates).

The overall **document burden** in CTIS must be reduced for all trials.

The **Master File (Core Document Dossier) principle** with reduced add-on demands e.g. for complex clinical trials must be installed in CTIS.

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2. Role of MedEthicsEU and harmonised procedures
MedEthicsEU is working with high priority towards the aim of harmonising the working and assessment **standards** for the different MRECs and MREC structures in the single EU Member States and will continue to do so for all risk category trials. The CTR should include a provision for **obligatory templates** e.g. for recruitment and informed consent process, participant information sheet and informed consent form, and others. Due to national laws these templates should contain

[1] https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/safety-reporting-during-clinical-medicinal-trials/~/media/041C4E3E801749389D5875C0CE991396.ashx
[2] https://legalinstruments.oecd.org/public/doc/281/281.en.pdf
[3] WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants – WMA – The World Medical Association
[4] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e6-r3-guideline-good-clinical-practice-gcp-step-5_en.pdf
[5] https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTCG/2025-04-CTCG-Q_A-on-Safety-Addendum-V2.pdf

a part which is uniform for the EU and another part for additional national legal requirements. The participant information letter and informed consent form should be ideally divided in a short central document with focus on understandability of the trial by potential trial participants and additional appendices having all legally required information (including national requirements). A clear task for MedEthicsEU for the content of the part II templates should be incorporated into the CTR.

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3. Reform the assignment process for Ethics Committees

While the single-entry CTIS is a strong tool for multinational trials, the **anonymous and random allocation** of MRECs in some MS should be replaced by a system better balancing the "conflict of interest" problem with the expertise of the MREC, thus reflecting the requirements of the Declaration of Helsinki (2024, Article 23). The process should allow deliberate assignment based on specialization and capacity.

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4. No general centralization of MREC assessment into one MREC for all EU MS

In general, the Ethics Review should remain in the ambit of the individual EU member states. Reasons are

- variations in cultural, social, and moral norms in the respective populations,
- different definitions of vulnerable populations,
- specific legal and healthcare structures,
- existing local expertise (DoH, article 23), and
- facilitation of public trust and engagement.

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5. Clarify core definitions

Key terms in Articles 1 and 2—such as "normal clinical practice", "low-intervention clinical trial", and "minimal additional risk or burden"—are vaguely defined and inconsistently applied. Their definitions should be revised. Responsibility and policy competence to define these terms must be delegated to the National and whereever possible the European Medical Societies (e.g. "normal clinical practice") and MRECs (e.g. "minimal additional burden").

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6. Simplify and streamline the regulatory framework

The **complexity of the CTR** has spawned a proliferation of secondary guidance, Q&As, best practices, and recommendations, creating a regulatory labyrinth for MRECs, sponsors, and investigators. A revised CTR must be self-explanatory, must focus on **clarity and usability**, with subsequently streamlined sublegal documents and practical tools for users including a **pilot** page helping the applicants to find answers for specific questions. None of the sublegal texts should impose additional restrictions on the flexibility of the CTR itself. The current fragmentation in published guidance, Q&As, and similar documents should be eliminated, with all information consolidated and maintained in a single central source.

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7. Use plain, precise language

Articles like 31 (incapacitated subjects) are written in overly complex, sometimes contradictory language. Clear, legally robust wording proposed by MREC legal experts should be adopted. The CTR should be aligned with the DoH (2024) in which it is stated that for vulnerable populations, the harms of exclusion must be considered and weighed against the harms of inclusion.

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8. Revise rigid provisions for trials on minors (Article 32)

The current article does not balance the "harm of exclusion" against the "harm of inclusion", as emphasized in the Declaration of Helsinki (see also point 7). This unwarranted rigidity risks denying children with life-threatening illnesses access to clinical trials and must urgently be revised.

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9. Add legal provisions for public health emergencies (PHE)
The CTR lacks clear, binding procedures for urgent responses to PHE. These must be codified at the legal level, not left to secondary guidance.

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10. Reconsider "serious breach" reporting (Article 52)
This provision has created significant confusion without clear evidence of benefit. It should either be removed or at least redefined, with the (Coordinating) Investigator with/without monitoring committee having final authority on what constitutes a serious breach.

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11. CTR/MDR/IVDR
A seamless synchronization of the CTR with the MDR/IVDR is important.

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12. CTIS – Key improvements needed

- CTIS functionality must be urgently improved to meet CTR Article 82. CTIS has still not achieved full functionality and does not meet the system functional specifications.
- Enable CTIS to operate efficiently, fostering trust in the system while minimizing administrative burden.

In addition, CTIS should support fit-for-purpose submissions of complex clinical trials.

At least, the following CTR changes impacting CTIS functionality improvements are needed:

- Synchronize timelines between Part I and Part II.
- Reinstate all procedural phases (validation, assessment, decision) in every workflow.
- Minimize workarounds, especially under Article 11.
- Permit parallel submission of SM Part II with all non-SM applications.
- Allow RMS role transfer to an MSC if the trial will not commence in the RMS's.
- Adjust RMS timelines after response sponsor to reinforce RMS authority on concluding part I .
- Enable expedited procedure functionality (eg support shorter timelines for the review of mononational trials (no coordinated review).
- Treat multiple MS additions as a single procedure, allowing added MSs to view and comment on Part I considerations of the added MS as in initial applications.
- Consider timeslots for better planning especially in periods with less resources (winter and summer break) on top of reinforcing fair workshare between MS.
- Consider the introduction of sponsor clock stops once a Request for Information is received will help ensure that sponsors have sufficient time to respond to critical issues, particularly those which require significant changes to core documentation such as the protocol and participant information materials. This could potentially greatly reduce the need for additional RFIs, the conditional approval of trials or trial rejection. This could overall help ensure that trials can start as soon as possible without the need for additional submissions or applications.
- Enforce timelines stipulated in CTR, prevent unwanted (but currently frequent) overruns.
- As a future objective registries with investigator CVs, DoI and other applicable documents should be made available within CTIS for MRECS and NCAs.

Conclusion
These targeted reforms will foster a leaner, risk-adapted regulatory environment that preserves patient safety, protects data quality, while restoring Europe's competitiveness as a site for clinical research. Since we only provide examples at this stage, we propose establishing a dedicated writing committee involving all major drivers of clinical trials: investigators, MREC representatives, industry representatives, NCAs, and patient advocates, to review the CTR article by article.

Board of MedEthicsEU, 18 September 2025

Recommendation of the Council on the Governance of Clinical Trials

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Background Information

The Recommendation on the Governance of Clinical Trials (hereafter, the "Recommendation") was adopted by the OECD Council on 10 December 2012 on the proposal of the Committee for Scientific and Technological Policy (CSTP). The Recommendation is intended to facilitate international co-operation in clinical trials on medicinal products, particularly for trials initiated by academic institutions. Its primary focus is on improving consistency among national regulations and their interpretations, and on streamlining procedures for the oversight and management of clinical trials, by introducing a proportionate regulatory approach, while enhancing the protection of participants in research trials.

The need for an international standard on the Governance of Clinical Trials

Clinical trials, including tests of new medicines or new therapies, as well as optimising existing medicinal products and procedures, are fundamental to improving health and welfare. This is especially important during worldwide emergency health crises, such as the recent COVID-19 pandemic, when these clinical trials have to be fast-tracked to produce results as quickly as possible. However, while medical investigators, particularly in the public research sector, are increasingly involved in international studies and collaboration, they continue to face a wide array of different regulatory mechanisms across countries. This, combined with the tight national regulations to ensure patient safety and methodological quality, has led to administrative complexity that has led many well-conceived clinical trials aimed at addressing important public health problems to either not be conducted or to be so delayed that their impact is reduced. This is particularly true for the conduct of international clinical trails that involve multiple centres, and for trials initiated by academic structures that may not have well developed administrative support.

It is with this in mind that the OECD Global Science Forum (GSF), a subsidiary body of the CSTP, has worked on a harmonised framework for the better international governance of clinical trials, in which requirements will be based on the risks associated with the study. The Recommendation was developed following extensive consultations and intensive work involving other OECD committees (Health Committee, Chemicals Committee, Environment Policy Committee), as well as relevant stakeholders such as Business at the OECD.

Scope of the Recommendation

The Recommendation contains a set of principles that Adherents should implement to develop a risk-based oversight and management methodology for clinical trials. These principles are built on two approaches:

- a stratified approach, generally based on the marketing authorisation status of the medical product, that can be applied in legislation or regulation in a common manner across countries, and
- a trial-specific approach that considers a large number of other issues such as additional diagnostic procedures, specific populations concerned, or informed consent.

This risk-based approach intends both, to facilitate international clinical trials and to help streamline the procedures for low-risk clinical trials.

For further information please consult:
http://www.oecd.org/sti/inno/oecdrecommendationonthegovernanceofclinicaltrials.htm.
Contact information: gsforum.contact@oecd.org.

Implementation

The 2020 Report on the implementation, dissemination and continued relevance of the Recommendation on the Governance of Clinical Trials, was approved by the CSTP on 9 September 2020. It demonstrates a growing awareness regarding the need to adopt a risk-based approach to oversight and management methodology in clinical research regulation. Although Adherents may still have different interpretations of risk-based regulatory processes, a very high percentage of those Adherents have started to adopt this approach.

Another important and positive element is that Adherents usually adapted their whole regulatory procedures to take into account the consequences of risk categories in the various elements of the regulatory approval process.

However, the Report also reveals a lack of standardisation of regulatory processes between Adherents, even when they have adopted a coherent risk-based approach. This is a major concern as such heterogeneity will continue to considerably hinder the development of international clinical trials, which are essential for evaluating treatments for rare diseases or during emergency crisis, such as the COVID-19 pandemic. The development of common international standards and procedures should, thus, be one area of the implementation process on which Adherents' focus should be particularly in the coming years.

The Report was developed by the GSF through an online questionnaire in 2018 – 2019, but the finalisation of the Report took place after the COVID-19 pandemic started, which allowed for discussions between Adherents on the role of the Recommendation to address the crisis. The key message emerging from the Report that resonates particularly loudly in the context of the COVID-19 crisis is that adopting harmonised risk categories – as proved for in the Recommendation – is a critical step in harmonising clinical trial regulations across countries. The COVID-19 crisis has demonstrated that failure in this regard constitutes a major obstacle to conducting essential clinical trials in response to pandemics.

THE COUNCIL,

HAVING REGARD to Article 5 b) of the Convention on the Organisation for Economic Co-operation and Development of 14 December 1960;

HAVING REGARD to the 2008 Helsinki Declaration on Ethical Principles for Medical Research Involving Human Subjects, and to the E6 guideline of the International Conference of Harmonisation for Good Clinical Practice;

RECOGNISING that clinical trials play a critical role in the development and evaluation of new and effective treatments of human diseases and therefore have a significant effect on public health;

RECOGNISING that the welfare and safety of patients and healthy volunteers participating in clinical trials must be duly ensured and their rights respected, in agreement with internationally recognised ethical rules;

RECOGNISING that the reliability of scientific data generated by clinical trials must be guaranteed, in order to ensure that medical practice is based on sound evidence;

RECOGNISING that many clinical trials are driven by pressing public health needs in areas where diseases and conditions affect only a small number of patients worldwide, or where treatments are not commercially viable, or where trials aim to improve existing procedures and prescribing practices, and that they increasingly involve multi-site international collaboration;

RECOGNISING that differences in national and regional regulations and their interpretation have led to very complex administrative processes, especially for multinational clinical trials;

RECOGNISING that national regulations that adopt uniform approaches regardless of the risk involved and of the objective of the trial may hamper the development of clinical trials, particularly those sponsored by non-profit groups such as universities, hospitals and charities;

RECOGNISING that more coherent and simpler administrative procedures for multinational clinical trials would be of great benefit to public health;

On the proposal of the Committee for Scientific and Technological Policy;

I. **RECOMMENDS** that Members adapt their national regulations and procedures to incorporate a risk-based methodology for the oversight and management of clinical trials, taking into account the principles set out in the Annex to this Recommendation, of which they constitute an integral part;

II. **INVITES** non-Members to adhere to this Recommendation;

III. **INSTRUCTS** the Committee for Scientific and Technological Policy to monitor the implementation of this Recommendation, review it in light of its impact on the quality of clinical trials and on the safety of clinical trial participants, and to report to Council within four years of its adoption and as appropriate thereafter.

ANNEX

I. OBJECTIVES AND SCOPE

This Recommendation is intended to facilitate international co-operation in clinical trials on medicinal products, particularly for trials initiated by academic institutions.

Its primary focus is on improving consistency among national regulations and their interpretations, and on streamlining procedures for the oversight and management of clinical trials, by introducing a proportionate regulatory approach, while enhancing the protection of participants in research trials.

Although this Recommendation is primarily driven by the need to facilitate co-operation among academic groups for clinical trials undertaken for non-profit purposes, Members may wish to extend the implementation of this Recommendation to the oversight and management of all clinical trials, thus adopting principles similar to those enumerated below regardless of the objective of the trial.

II. PRINCIPLES

Members should implement a risk-based oversight and management methodology for clinical trials reflecting the following principles for risk assessment. These principles combine (A) a stratified approach, generally based on the marketing authorisation status of the medical product, that can be applied in legislation or regulation in a common manner across countries, with (B) a trial-specific approach that considers a large number of other issues such as additional diagnostic procedures, specific populations concerned, or informed consent.

A. Stratified approach

A.1. Risk categories

Members should introduce a definition of risk categories for clinical trials in their legislative or regulatory framework, in line with the following three categories that use the marketing authorisation status of medicinal products to determine the level and uncertainty of risk:

Category A concerns clinical trials on authorised medicinal products (according to national or regional regulations) tested in accordance with their marketing authorisation.

Category B concerns clinical trials on authorised medicinal products tested according to treatment regimens outside their marketing authorisation (in terms of population, condition, administration, or dosage):

1. supported by published evidence or guidance or established medical practice;

2. not supported by published evidence or guidance or established medical practice.

Category C concerns clinical trials on medicinal products without any marketing authorisation.

Members should also take into account the following product-related modulating factors when assigning one of the above categories or subdivisions thereof to a clinical trial, as they may impact the risk assignment, and result in an upgrade or downgrade of the risk level:

- novelty of the medicinal product and/or of its class (including new formulation of a marketed substance);
- innovative nature of the treatment (e.g. advanced therapy/biologics);
- marketing authorisation obtained in other countries.

A.2. Risk assessment

The risk categorisation for an individual trial should be proposed by the investigator and/or sponsor, and later validated by appropriate approval or oversight bodies. These approval or oversight bodies should have access, whenever needed, to external expertise, particularly through requests to the regulatory bodies regarding the status of the medicinal product, and through requests to clinical experts regarding the accepted standard of care.

A.3. Impact of risk categorisation on the oversight and management of clinical trials

Members should ensure that the oversight and management processes of the clinical trials are adapted to the risk category. More specifically:

A.3.1 Ethical review and informed consent

As specified in the Declaration of Helsinki and in the International conference of Harmonisation (ICH) E6 guideline, Members should require that ethical review and approval of the protocol by a research ethics committee or institutional review board be carried out for every trial, regardless of its risk category. Informed consent from every trial participant should be required as a rule regardless of the risk category (exceptions may be granted in specific situations, as described in the provisions of the 2008 Declaration of Helsinki).

A.3.2 Approval of trial by regulatory bodies

Members should require approval by the appropriate regulatory bodies, for instance the Competent Authority, for category B and C clinical trials.

Members may decide not to require prior approval from regulatory bodies for category A clinical trials.

Members should ensure that regulatory bodies are able to access information through trial registration and that they can request further information if needed, or perform inspections. Members should strongly encourage public registration of the key items (including the 20 WHO ICTRP items and the risk category) of every trial before enrolment of participants, providing open access to information on ongoing trials for patients, investigators, researchers, health professionals, sponsors, ethics committees, competent authorities, funding agencies, and health authorities.

A.3.3 Safety reporting

Members should ensure that safety reporting in clinical trials on medicinal products includes, regardless of the risk category, periodic reports to the appropriate oversight bodies of serious adverse events. They should also provide for expedited reporting of unexpected serious adverse reactions to the appropriate oversight bodies having the capacity to detect safety signals, regardless of the risk category. However, adaptations should be possible based on the protocol of each individual trial (see B.3.3).

A.3.4 Indemnification and insurance

Members should ensure that their regulatory framework takes into account the risk categories for the purpose of indemnification and insurance. Members should in particular explore how the coverage of patients in investigator-driven clinical trials in the lower risk categories (products being used in approved indications, or used outside licensed indications in established treatment regimens, corresponding to categories A and Ba) could be achieved through indemnification by the national health services or health insurance system, product liability (for category A), investigator or institution liability, without requiring a specific trial insurance. However, patients and healthy volunteers should not bear the cost of any negligent or unforeseen harm related to their participation in clinical trials.

A.3.5 Management of medicinal products

Members should ensure that the cost of medicinal products in categories A and Ba clinical trials is borne by the same bodies as those bearing the costs in cases where the therapy is used outside the context of a clinical trial.

Members should make it possible to use cost-effective techniques for the labelling and tracing of investigational medicinal products for category A trials (and optionally for category B). Depending on the study objective and protocol, it should be possible to distribute the medicinal product from the shelf, with or without a trial-specific label.

Members should allow pharmacies to repackage and re-label medicinal products without specific Good Manufacturing Practice (GMP) authorisation in category A and B trials.

A.3.6 Documentation

Members should allow for category A and B clinical trials to adapt the trial master file and replace the investigator brochure by the summary of product characteristics. No Investigational Medicinal Product (IMP) dossier should be required for category A and cross-reference should be allowed for category B.

B. Trial-specific approach

Members should implement a complementary trial-specific approach to guide the operational processes of each clinical trial in addition to the general stratified approach.

B.1. Risk assessment principles

Sponsors, service providers, investigators, patient representatives, ethics committees and health authorities should develop common risk assessment tools to support the risk assessment of individual trials, enabling their use in multinational studies. Risk assessment tools should cover the main risk determinants, including:

I. Risk to patients' rights:

1. information and informed consent
2. personal data protection

II. Risk to patients' physical integrity and safety:

1. safety of the treatment intervention
2. risk of diagnostic intervention
3. vulnerability of the patient population

III. Risk to data integrity and public health:

1. data quality, data management and analysis, data access and publication
2. credibility of results
3. impact on public health

Risk assessment in clinical trials should be considered as a dynamic process, and be continuously reviewed and updated during the conduct of the trial. This process should take into account, in particular, amendments, deviations, or safety events and results of relevant data generated outside the study.

To promote uniformity and coherence in risk assessment, Members should organise training of risk assessors such as sponsors, investigators, ethics committees or Institutional Review Board, competent authorities, insurance companies, or patients' representatives.

B.2. Risk assessment procedure

Assessment of risk in a trial should be undertaken early in the process, in parallel with the development of the protocol, to ensure that the trial design, risk mitigation, and trial management plans included in the protocol take risk fully into account.

The level of risk to patients' rights and physical integrity and safety for a given trial should be assessed in light of the potential benefit associated with the research.

The nature and extent of risks associated with an individual trial should be assessed by the investigator and/or the sponsor.

B.3. Risk-adaptation and risk mitigation

The nature and extent of risks associated with each individual trial should impact the supervision and management processes of the clinical trial, and result in adapted provisions for risk mitigation.

B.3.1 Ethical review and informed consent

As stated in A.3.1, Members should ensure that ethical reviews and the collection of individual informed consents are not affected by the nature and extent of risks and follow the principles articulated in the 2008 Declaration of Helsinki and the ICH E6 guideline.

B.3.2 Approval by regulatory bodies

It should be possible to adapt the content of the application dossier based on the protocol of the individual trial.

B.3.3 Safety reporting

It should be possible to adapt the adverse event reporting requirements to the individual trial, to the nature of the intervention and cumulated previous experience, and to the medical condition of the patient population. It should also be possible, in agreement with the appropriate regulatory bodies, to include specific provisions in the trial protocol for the reporting of some types of foreseeable adverse events to be waived. The requirement for a Data Safety and Monitoring Board should also be linked to the nature of the trial.

B.3.4 Management of the medicinal product

Given that the objective of the trial and the risk assessment may affect the traceability of the medicinal product, labelling should take into account the particularities of the trial, the blinding procedure, the way of administering the medicinal product and the characteristics of the patient population. Treatment compliance regimes should also be adapted in line with the objectives of the clinical trial.

B.3.5 Indemnification/insurance

Indemnification/insurance provisions and costs, where required, should be proportionate to the risk to participants' integrity and safety. Risk assessment principles similar to those described in principle B.1.II should be used to determine the nature and extent of risk to patients’ physical integrity and safety. Common risk assessment tools should be developed to help assess risks in a manner that is consistent across locales.

B.3.6 Quality management

Trial quality management should adapt to the particularities of the trial and to the nature and extent of risks. Risk assessment should identify the key trial parameters. Quality management plans should focus on mitigating key risks.

B.3.7 Control procedures

Inspections, audits and monitoring should be established in a manner that is proportionate to the risk stratification and trial-specific assessment, and take into account the provisions made to take these risks into account.

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Since the creation of the OECD in 1961, around 460 substantive legal instruments have been developed within its framework. These include OECD Acts (i.e. the Decisions and Recommendations adopted by the OECD Council in accordance with the OECD Convention) and other legal instruments developed within the OECD framework (e.g. Declarations, international agreements).

All substantive OECD legal instruments, whether in force or abrogated, are listed in the online Compendium of OECD Legal Instruments. They are presented in five categories:

- **Decisions** are adopted by Council and are legally binding on all Members except those which abstain at the time of adoption. They set out specific rights and obligations and may contain monitoring mechanisms.

- **Recommendations** are adopted by Council and are not legally binding. They represent a political commitment to the principles they contain and entail an expectation that Adherents will do their best to implement them.

- **Substantive Outcome Documents** are adopted by the individual listed Adherents rather than by an OECD body, as the outcome of a ministerial, high-level or other meeting within the framework of the Organisation. They usually set general principles or long-term goals and have a solemn character.

- **International Agreements** are negotiated and concluded within the framework of the Organisation. They are legally binding on the Parties.

- **Arrangement, Understanding and Others**: several other types of substantive legal instruments have been developed within the OECD framework over time, such as the Arrangement on Officially Supported Export Credits, the International Understanding on Maritime Transport Principles and the Development Assistance Committee (DAC) Recommendations.

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The Danish Medicines Agency's guidance on risk-based recording and reporting of adverse events in clinical trials on medicinal products under Regulation (EU) no. 536/2014

Table of contents

1. Introduction

The recording and reporting of adverse events is a critical process for safeguarding the safety of participants in a clinical trial and essential for ensuring the evidence and accuracy of a medicinal product's safety profile. However, it is acknowledged that the collection and reporting of adverse events can be resource-consuming for both the investigator and sponsor and therefore should be risk-adjusted based on the added value gained from collecting the adverse event data.

Detailed recording of adverse events is particularly important for medicinal products that are not yet authorised, and where the data on the medicinal product's safety profile are insufficient. In contrast, clinical trials involving well-established authorised medicinal products contribute less with new significant safety data.

Article 41(2) of the legislation on clinical trials with medicinal products, regulation (EU) No 536/2014 of 16 April 2014 (CTR)[1] allows adaptation of adverse event management[2] in relation to the individual protocol:

REGULATION (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use:

CHAPTER VII, Article 41(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."

In practice, this means that the clinical trial adverse event management can be adapted based on the trial's specific design and purpose. Risk adaptation of adverse event management must be solid justified within the protocol with patient safety and the integrity of trial data remaining as the top priorities.

This guidance describes the requirements and processes needed for implementing risk-adapted adverse event management.

In the case of clinical trials serving a regulatory purpose (e.g. an indication extension or marketing authorisation), reference is also made to the *ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials*[3].

[1] More information about the clinical trials regulation is provided on the website of the Danish Medicines Agency.
[2] The term 'adverse event management' will be used in this guidance document as a collective term for recording and reporting of adverse events.
[3] ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials is available on the European Medicines Agency's website.

For general considerations on the risk assessment of clinical trials, please refer to the *Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (25 April 2017)*[4].

2. Requirements in relation to risk adaptation in adverse event management

Sponsors intending to apply any risk adaptation in adverse event management in clinical trials should pay attention to the following:

1. Any risk-adapted adverse event management must be justified in relation to the specific trial's purpose, design and risk assessment. The protocol must include a clear justification along with a detailed description of the risk-based approaches, including a description of the processes in place for adverse event management. Guidance on these areas is given in the following sections:
   - Process for assessing adverse events in a clinical trial (section 3)
   - Risk assessment of a clinical trial (section 4)
   - Risk-adapted adverse event management in a clinical trial (section 5)

2. The sponsor must establish whether the medicinal products included in a clinical trial are subject to stricter national reporting requirements and/or additional monitoring in the EU. Risk adaptation is usually not possible for authorised medicinal products subject to stricter reporting requirements or additional monitoring. In case of risk-adapted adverse event management, the sponsor must confirm in the protocol that the medicinal products in a clinical trial are not subject to stricter national reporting requirements in the concerned Member States involved in the clinical trial or additional monitoring in the EU. The medicinal products subject to stricter reporting requirements in Denmark is available in the list published by the Danish Medicines Agency. The list of medicines under additional monitoring in the EU is available on the European Medicines Agency's website.

3. Risk-adapted adverse event management may only be implemented in relation to the recording and reporting of adverse events and adverse reactions from investigator to sponsor. For information about the sponsor's reporting obligations, reference is made to the requirements of the CTR[5].

4. Clinical trials investigating diseases with high morbidity or mortality may have primary or secondary efficacy endpoints that fall under the definition of a suspected unexpected serious adverse reaction (SUSAR). In such trials, according to CTR Annex III, section 2.5 point (21), it may be justified to designate specific serious events as disease-related and exempt them from SUSAR obligations. This in order to avoid systematic unblinding and to maintain the integrity of the trial data. In such cases, a Data Safety Monitoring Board (DSMB) should be established to monitor unblinded data. If a DSMB is not established, it must be justified how continuous safety monitoring is ensured in some other way. It may also be justified to exempt the same serious events from immediate reporting by the investigator to the sponsor. However, this requires an alternative procedure to ensure that the DSMB has continuous access to complete safety data.

[4] Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (25 April 2017) is available at EudraLex - Volume 10 - Clinical trials guidelines.

[5] The sponsor's obligations in relation to reporting to the authorities are provided in articles 42 and 43 of CTR 536/2014.

5. The annual safety report (ASR) must describe the risk-adapted approaches under which the ASR has been prepared. The sponsor is obligated to include all serious adverse reactions (SARs) and all suspected unexpected serious adverse reactions (SUSARs) in the ASR. If there are exemptions to immediate reporting of serious adverse events to the Sponsor, it is important to note that all registered serious adverse events must still be reported to the sponsor, in a timely manner, for the sponsor to include all the registered serious events in the ASR. The protocol must also state if a single safety report is submitted for all investigational medicinal products used in the clinical trial, see article 43(2) of the CTR.

6. Adverse events exempted from recording are not expected to be documented elsewhere. However, the investigator remains responsible for ensuring that the trial participants' medical records are continuously updated with clinically relevant information for healthcare professionals who are otherwise involved in the patients' present or future care and treatment. During GCP-inspections particular attention may be given to how medical records entries are handled.

The protocol template published by the Danish Medicines Agency can be used to prepare the protocol. The template describes the particulars to be included in the protocol for compliance with the CTR.

3. Process for assessing adverse events in a clinical trial

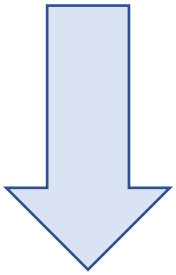
It is essential for the safety of trial participants and the data integrity, that the sponsor, investigator and other relevant staff understand and have received training in the processes for assessment, recording and reporting of adverse events. The processes for assessment of adverse events and the definitions of relevant terms must therefore be sufficiently described in the protocol.

The process for assessing whether it is a serious adverse event (SAE), a serious adverse reaction (SAR) or a suspected unexpected serious adverse reaction (SUSAR) is described below (Figure 1). You will find the full flow chart for assessment of all events in Appendix 1 and a description of relevant terms in Appendix 2.

These processes must be in place irrespective of whether risk-adapted recording and reporting of adverse events is implemented.

Figure 1. Assessment of serious adverse events and adverse reactions.

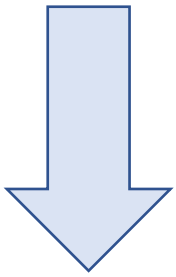
SAE (serious adverse event)	A serious adverse event (SAE) means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.



Causality assessment – is the serious adverse event related to the investigational medicinal product?
In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product (IMP) based on an analysis of available evidence.

See the reference provided in Appendix 2 for guidance on the causality assessment

SAR (serious adverse reaction)	A serious adverse reaction (SAR) is an SAE that is assessed to be related to the IMP, i.e. the treatment administered in the clinical trial.



Is the serious adverse reaction expected or unexpected?
The determination of whether an event is expected or unexpected is assessed based on the reference safety information (RSI).

Example: In the case of authorised medicinal products, the RSI is often section 4.8 of the summary of product characteristics (SmPC). Therefore, an adverse reaction appearing in the SmPC section 4.8 is expected, and an adverse reaction not appearing in section 4.8 of the SmPC is unexpected.

SUSAR (suspected unexpected serious adverse reaction)	A suspected **unexpected** serious adverse reaction means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the RSI.
ASR (annual safety report)	Annual safety report: It is expected that any relevant safety information will be described in the annual safety report. The report is expected to include a list of SARs and SUSARs and an assessment of whether these events give rise to updating the protocol. Likewise, the annual safety report is expected to include an assessment of whether the benefit-risk balance is changed or unchanged, meaning if the trial may continue or if a protocol amendment is required for it to continue.

Annual safety reports must be prepared and reported for all trials

Once a year, the sponsor must summarise cumulative safety information in the annual safety report. Based on this report, the safety of the trial is evaluated, including if the benefit-risk balance has changed and whether, on the basis thereof, the trial may continue. The annual safety report ensures the continuous safety assessment and may therefore not be exempted despite any applied risk-adapted adverse events management.

The annual safety report must describe the risk-adapted approaches as provided in the clinical trial protocol, under which the report has been prepared.

4. Risk assessment of a clinical trial

The level needed for adverse event recording and reporting depends on the evidence base of the investigated medicinal product. As mentioned earlier, risk-adapted adverse event management must be justified on the basis of a trial-specific risk assessment.

A risk assessment means the identification of potential risks associated with the concerned trial, based on the safety of the participants, the investigational medicinal product and the trial design and methods. A number of different factors influence the extent to which the safety of the trial participants is affected in the trial, e.g. the status, type and safety profile of the medicinal product, the difference between intervention and normal clinical practice, and the complexity of the trial. The risk assessment and the associated risk categorisation of a trial are described below in Figure 2, points 1-4.

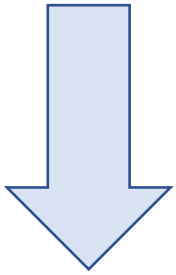
Figure 2. Risk assessment of a trial for the purpose of applying risk-adapted adverse event management.

1) Consider the RISK FACTORS likely to impact the safety of the trial participant

At least the following points must be considered and addressed in a risk assessment:

- Whether the medicinal product is authorised, including the total exposure of the medicine and whether the available safety data of the medicinal product provides sufficient grounds to implement risk-adapted adverse event management.
- The type of medicinal product/intervention (e.g. mechanistic characteristics, pharmaceutical form, route of administration).
- Indication, including the difference between intervention and normal clinical practice.
- Population, including age, gender and other patient characteristics.
- Dose and treatment regimen compared to the authorised dose and treatment regimen described in the product information, including the use of combination therapy or other medicines given concurrently, including an assessment of whether this may lead to serious or more frequent adverse reactions, new adverse reactions or new drug interactions.
- Complexity of the trial design.

See Appendix 3 for more considerations of risk factors likely to impact the safety of trial participants.



2) Assess the RISK LEVEL based on the difference between intervention and normal clinical practice

What is the risk posed to the patient compared to the standard treatment?
What are the risks, and how can they be handled?

INCREASED RISK FOR PATIENTS

"Low-risk" trial = **risk level 1**	**"Medium-risk"** trial = **risk level 2**	**"High-risk"** trial = **risk level 3**
➢ The investigational medicinal product(s) is/are authorised ➢ The intervention is comparable to standard treatment ➢ The intervention and the medicinal product's evidence base and safety profile are robust, also in relation to rare adverse reactions ➢ Expected new signals are minimal Application of risk-adapted adverse event management can generally be justified. See examples in Appendix 4.	➢ The investigational medicinal product(s) are authorised, but are used for an unapproved indication ➢ The intervention is not significantly different from the standard treatment, and the safety profile is expected to be comparable ➢ The safety profile of the medicinal product is robust Application of risk-adapted adverse event management can be justified if based on a trial-specific risk assessment. The risk assessment and justification should address the risk factors listed under point 1) of this figure. See examples in Appendix 4.	➢ Investigational medicinal product or indication is not authorised ➢ The intervention has not been studied before or is significantly different from the standard treatment ➢ The intervention and the safety profile of the medicinal product have not been sufficiently studied, and evidence on the efficacy and safety of the product is insufficient ➢ The investigational medicinal product is authorised but subject to stricter national reporting requirements or additional monitoring. See point 2 in section 2. Thorough adverse event management is needed to safeguard patient safety and to ensure the collection of data on the safety profile of the medicinal product. Full adverse event management is expected, unless adaptation can be justified on robust grounds based on a trial-specific risk assessment. See examples in Appendix 4.

3) Assess if risk-adapted adverse event management may be justified

Based on the above risk assessment, a risk-adapted approach to recording and reporting of adverse events may be possible if sufficiently justified.

Even so, borderline cases may exist, which means that an assessment of the individual protocol and trial design is needed to determine the required level of adverse event management. In borderline cases, variables like the duration of treatment, whether or not a life-threatening disease is involved, knowledge of the product's mechanistic effects, as well as non-clinical signals, along with data from the clinical development and the total exposure of the medicinal product, may determine which approach is justifiable. This must be seen in the context of the robustness of the safety profile, also in relation to rare adverse events.

If there are doubts about whether the evidence base of the product's safety is sufficiently known or whether the intervention may expose the patient to a risk, conservative/full adverse event management must be applied.

See section 5 on risk adaptation in the management of adverse events.

4) Dedicate a section in the protocol specifically to the justification of risk-adapted adverse event management

This justification must at least include the following:

- Risk assessment of the trial and justification of the level of risk chosen for the trial.
- Description of risk-adapted adverse event management, including reasons why certain SAEs are not be recorded or not immediate reported to the sponsor.
- Considerations about the risks associated with the chosen risk-adapted adverse event management:
  - For trial participants?
  - For data integrity?
- How risks in the trial can be prevented and/or reduced?

The extent of the justification depends on the level of risk associated with the trial.

5. Risk-adapted adverse event management in a clinical trial

In general, all adverse events must be recorded and all serious adverse events must be reported to the sponsor, unless the risk-adapted adverse event management is supported by the risk assessment documented in the protocol.

Authorised medicinal products have generated a sufficient evidence base for their use with respect to the populations and indications as described in the SmPC, and the safety of authorised medicinal products is monitored on an ongoing basis (see Appendix 5). In relation to clinical trials with authorised medicinal products, it may therefore be possible to adapt recording and reporting of adverse events proportionate to the risk level of the trial. Conversely, it can usually not be justified to reduce the recording and reporting of adverse events for trials with non-authorised medicinal products.

The protocol must always provide justification for any risk-adapted approach on the basis of a trial-specific risk assessment and if there is a risk of new, more serious or more frequent adverse reactions. Regardless of the selected approach, the investigator must always have the possibility of recording any event and reporting these to the sponsor if the investigator finds this relevant/necessary.

The possibility of applying a risk-adapted approach to the recording and reporting of adverse events and adverse reactions from investigator to sponsor is described below in Table 1 and Tabel 2. SUSARs must always be reported by the sponsor to the EudraVigilance database regardless of the risk-adaptation applied to adverse event management, as stipulated in the CTR[6]. Likewise, the sponsor is required to submit annual safety reports (ASRs) via CTIS[7].

Table 1. Risk-adapted adverse event management based on the level of risk associated with the trial

Risk level:	**Risk level 1 = "Low"**	**Risk level 2 = "Medium"**	**Risk level 3 = "High"**
Recording of adverse events			
Is risk-adaptation for **AE recording possible**?	YES – AE recording can be exempted	YES – AE recording can be exempted	NO[b)] – all AEs must be recorded
Is risk-adaptation for **SAE recording possible**?	YES – SAE recording can be exempted	YES[a)] – SAEs pursuant to a predefined list in the protocol can be exempted from recording	NO[b)] – all SAEs must be recorded
Is risk-adaptation for **SAR recording possible**?	YES – only suspected unexpected serious adverse reactions (SUSARs) must be recorded	YES[a)] – SARs pursuant to a predefined list in the protocol can be exempted from recording	NO[b)] – all SARs must be recorded
Reporting of serious adverse events from investigator to sponsor			
Is risk-adaptation for **SAE reporting to sponsor possible**?	YES – SAE reporting can be exempted	YES[a)] – immediate reporting of recorded SAEs can be exempted, but must be reported to the ASR	NO[b)] – all SAEs must be reported immediately to sponsor
Is risk-adaptation for **SAR reporting to sponsor possible**?	YES – only suspected unexpected serious adverse reactions (SUSARs) must be reported immediately to sponsor	NO[b)] – all recorded SARs must be reported immediately to sponsor	NO[b)] – all SARs must be reported immediately to sponsor
Sponsor's reporting obligations			
SUSAR reporting	SUSARs must always be reported by the sponsor to the EudraVigilance database.		
Annual safety report (ASR)	The ASR must always be submitted by the sponsor via CTIS. See also section 3.		

[a)] Must always be justified based on the trial-specific risk assessment

[b)] Generally not possible, unless robust justification provided

[6] Find more information about reporting to the EudraVigilance database on the website of the Danish Medicines Agency.

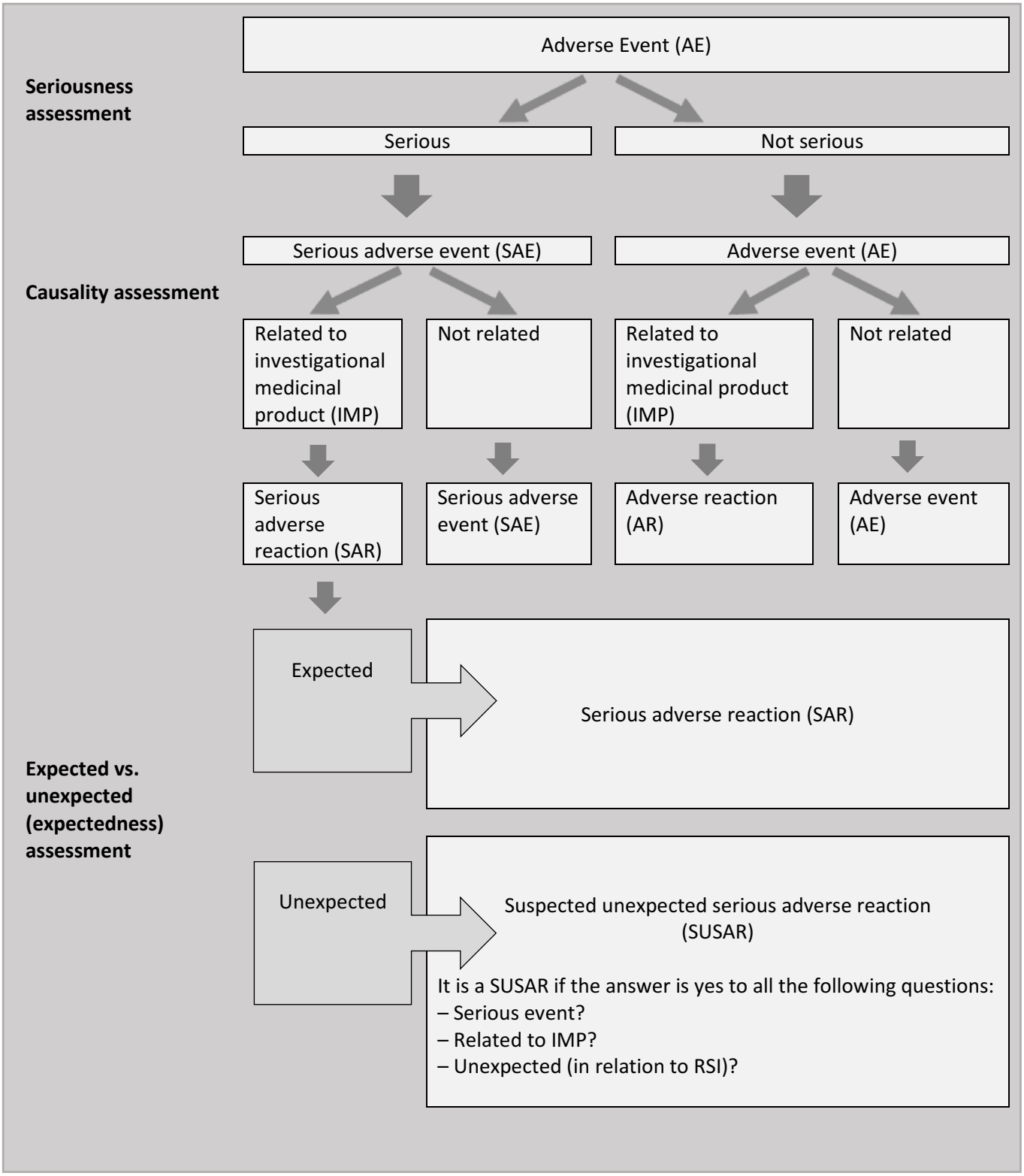
[7] Clinical Trials Information System (https://euclinicaltrials.eu/)

Tabel 2. Description of risk-adapted adverse event management.

Description of risk-adapted adverse event management based on the risk level	
Adverse event management at <u>risk level 1:</u>	The investigator must at least record adverse events satisfying all the following three criteria: 1) The adverse event must be serious (serious adverse event, SAE) 2) The adverse event must be suspected to be related to the investigational medicinal product (serious adverse reaction, SAR) 3) The adverse event must <u>not</u> appear in section 4.8 of the summary of product characteristics. In reality, it is the investigator who must assess expectedness when only suspected unexpected serious adverse reaction (SUSARs) are to be recorded. The investigator must report all recorded adverse reactions (subject to the above requirements) to the sponsor within 24 hours. The investigator must always have the possibility of recording and reporting any event to the sponsor if the investigator finds this relevant/necessary and this must be stated in the protocol.
Adverse event management at <u>risk level 2:</u>	In general, all SAEs must be recorded, but the sponsor may include in the protocol a predefined list of SAEs not to be recorded. This could be SAEs either associated with the investigational medicinal product or an underlying disease. SAEs in this category could be administrative/planned hospitalisation, exacerbation of underlying disease, or in the case of the treatment of intensive-care patients expected to have a critical disease course involving, for example, multiple organ failure. SAEs that are related to the investigational medicinal product (=SARs) and are listed in section 4.8 of the product information (known adverse reactions) may generally be exempted from recording. In case of that other SARs than expected (known adverse reactions, see 4.8 of the product information) will be exempted from recording, this must be further justified. Any SAEs and/or SARs exempted from the recording must always be clearly stated and justified in the protocol. The reporting of SAEs to the sponsor within 24 hours can be omitted, if predefined in the protocol and justified. However, all SAEs recorded and deemed related to the intervention (causal relationship) must be reported immediately to the sponsor. In other words, <u>all recorded SARs</u> must be reported to the sponsor within 24 hours. If SARs are exempted from immediate reporting due to the fact that they are recorded as part of the clinical trial's primary or secondary efficacy endpoints, continuous safety monitoring must be ensured through a DSMB. Please see point 4 in section 2. For SAEs exempted from immediate reporting, it is important to note that all SAEs recorded but not reported immediately, must still be reported to the sponsor no later than before preparation of the ASR, and the specific frequency of reporting must be stated and justified in the protocol. The investigator must always have the possibility of recording and reporting any event to the sponsor if the investigator finds this relevant/necessary and this must be stated in the protocol.
Adverse event management at <u>risk level 3:</u>	It is expected that all AEs/SAEs are recorded, and that all SAEs/SARs are reported to the sponsor within 24 hours. Risk-adaptation is in general not possible, unless the sponsor can provide a robust justification based on a trial-specific risk assessment.

6. Appendix

Appendix 1 – Assessment of events and adverse reactions in a clinical trial



Appendix 2 – Description of selected terms

Adverse event (AE):

Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

Seriousness criteria:

The event is serious if at least one of the following criteria applies:

- *inpatient hospitalisation or prolongation of existing hospitalisation*
- *results in persistent or significant disability or incapacity*
- *results in a congenital anomaly or birth defect*
- *is life-threatening*
- *results in death*

Serious adverse event (SAE):

Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

Causality assessment:

A causality assessment is used to assess if an event is related to investigational medicine/intervention or not. In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence.

In the absence of information on causality provided by the reporting investigator, the sponsor shall consult the reporting investigator and encourage him to express an opinion on this issue. The causality assessment given by the investigator shall not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report.

The WHO-UMC's method may be used to make the causality assessment:
https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf

Serious adverse reaction (SAR):

Is an SAE in which the event is assessed to be related (see causality assessment) to the investigational medicine and/or intervention.

Suspected unexpected serious adverse reaction (SUSAR):

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information. Whether an incident is unexpected or expected is determined based on the reference safety information.

Reference safety information (RSI):

The determination of whether an event is expected or unexpected is assessed in relation to the reference safety information (RSI). Often, parts of the product information or parts of the Investigator's Brochure (IB) are used as RSI for the investigational medicinal product.

Example:
In the case of authorised medicinal products, the RSI is often a part of the summary of product characteristics (SmPC), i.e. an adverse reaction appearing in the SmPC, often section 4.8, is expected; an adverse reaction not appearing in the product information is unexpected.

Annual safety report (ASR):

Any relevant safety information is expected to be described in the annual safety report. A list of SARs and SUSARs is expected, including an assessment of whether these events give rise to updating the protocol.

The annual safety report must describe the risk-adapted approaches subject to which it has been prepared.

Likewise, the annual safety report is expected to include an assessment of whether the benefit-risk balance has changed or is unchanged, meaning if the trial may continue or if protocol amendments are required for it to continue.

It is possible to submit a single safety report on all investigational medicinal products used in a clinical trial, see article 43(2) of the CT regulation.

Appendix 3 – General considerations about risk factors and risk minimisation measures

The following may be considered in connection with the risk assessment (list is non-exhaustive):

- Does the trial population consist of healthy trial subjects or patients?

- Is the investigational medicinal product authorised, and is it used in compliance with what has been approved and described in the product information? If not, consider the following:
  - *Are there changes to the dosage regime/route of administration?*
  - *Are there changes to the population/indication?*
  - *How will these changes impact the safety of trial participants?*

- What are the known/expected risks, both in relation to the trial design and/or the investigational medicinal product?
  - *Have these risks been addressed in normal clinical practice?*
  - *If the adverse reaction profile of the investigational medicinal product is unknown, which risks are expected based on non-clinical data and/or based on the knowledge from other medicinal products containing the same active substance?*
  - *Is the duration of treatment supported by previous experience?*
  - *Is there a risk of dosing errors?*

- Are there any risks of interactions with other treatments given concurrently that could increase the risk to trial participants?

- Is there a need for further safety monitoring of the trial participant in addition to that provided in standard treatment? This could be additional laboratory tests, ECG, imaging, biopsy, more frequent visits to the doctor.

- Are further risk minimisation measures needed? The following may be considered:
  - *Restrictive inclusion and exclusion criteria, e.g. exclusion of persons with a particular risk due to secondary diseases, resulting from impaired kidney/lung/heart/liver function or the use of certain medicinal products.*
  - *Adjustment of treatment regimen and duration, including sufficient monitoring and facilities, rescue medicine and the presence of trained (emergency) staff when relevant.*
  - *Stopping criteria or (dose) modification of the investigational treatment, e.g. using a protocol-specified treatment algorithm or an independent Data Safety Monitoring Board (DSMB).*
  - *Focused recording of adverse events and adverse reactions, e.g. organ-specific events or events giving cause for specific concern; reporting to the sponsor and authorities must comply with the legislative requirements at all times.*
  - *Further safety monitoring, e.g. by way of experts in the disease, in its routine treatment and in the investigational medicinal product/study treatment; an independent DSMB for the assessment of new safety data and benefit-risk balance.*

Appendix 4 – Examples of clinical trials at the different risk levels

Examples "low-risk" trials (risk level 1):

- Low-intervention trials[8]
- Trials with authorised medicinal products involving an approved indication in which the intervention is normal clinical practice.
- Trials with authorised medicinal products involving a well-established off-label indication which is normal clinical practice and supported by published evidence.

Examples of "medium-risk" trials (risk level 2):

- Trials with authorised medicinal products involving an unapproved indication in which the studied indication/population/treatment DOES NOT differ significantly from the authorised indication or normal clinical practice, and where the safety profile is expected to be the same.
- PK/PD trials with data available from other authorised medicinal products in the same pharmacological class.

Examples of "high-risk" trials (risk level 3):

- Trials with non-authorised medicinal products or authorised medicinal products with limited knowledge about adverse reactions[9].
- Trials with authorised medicinal products involving an unapproved indication in which the studied indication differs significantly from the approved one, e.g. another disease area or a special population such as children for which the safety profile of the intervention has not been established despite the status of the medicinal product.
- Trials with combination treatment with two or more medicinal products, posing a risk of drug interactions and where it is not possible to break down the adverse event management on the individual medicinal products.
- Trials with modified medicinal products without a marketing authorisation, for example a new formulation/pharmaceutical form.
- Trials in which the medicinal product is used in combination with medical devices or other medicinal products with an expected synergistic effect (e.g. electroporation).

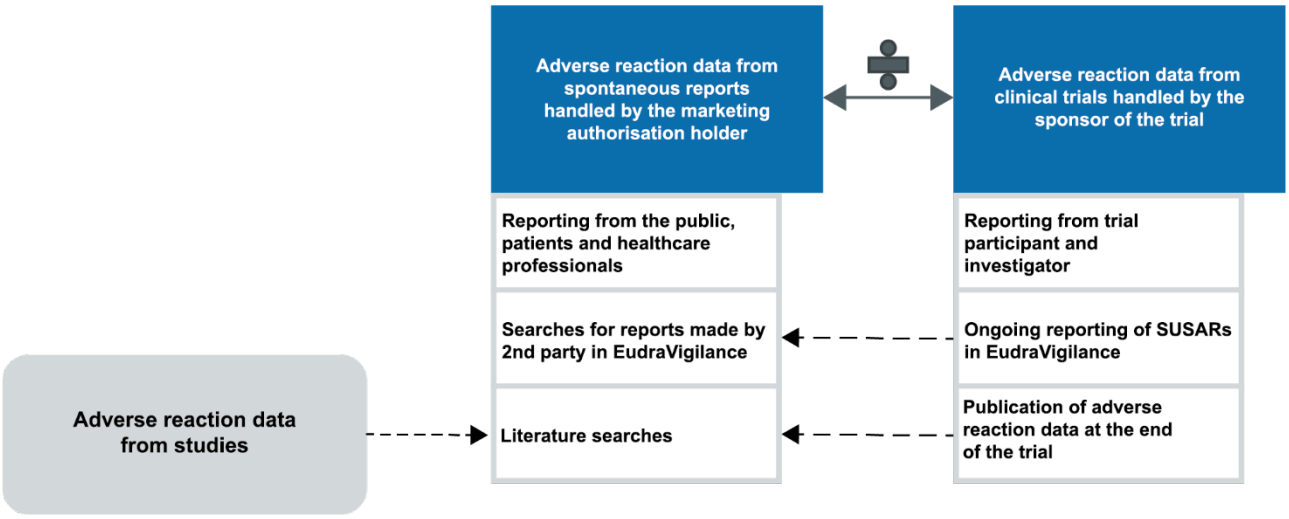
[8] Under article 2(3) of the CTR, a low-intervention clinical trial is a clinical trial which fulfils all the following conditions:
   a. the investigational medicinal products, excluding placebos, are authorised;
   b. according to the protocol of the clinical trial, i) the investigational medicinal 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;

[9] Including authorised medicinal products subject to additional monitoring and stricter reporting requirements

Appendix 5 – Evidence generation and data sources for authorised medicinal products

Medicinal products used in clinical trials are categorised as investigational medicinal products whether or not they have a marketing authorisation. Consequently, adverse event data collected in a clinical trial are not automatically sent to the marketing authorisation holder. Instead, alternative mechanisms ensure that the marketing authorisation holder can gain a complete overview of emerging safety data. One such mechanism is the sponsor's ongoing reporting of SUSARs to EudraVigilance database which are searchable by the marketing authorisation holder. Another mechanism is the literature searches made by the marketing authorisation holder which aim to identify publications containing safety data related to the concerned medicinal product (Figure 3).

Figure 3 Safety data sources for authorised medicinal products



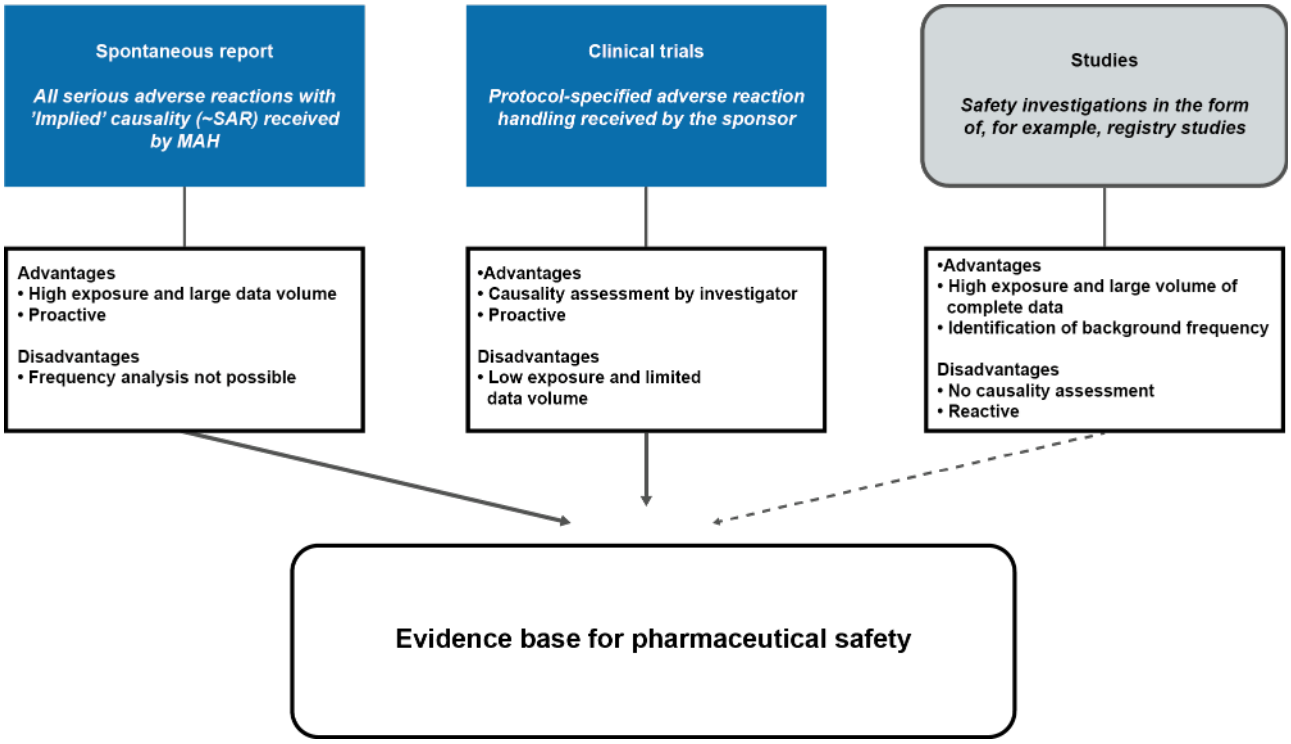
As illustrated in the figure above, literature searches will also identify adverse reaction data from other sources, such as registry-based studies. This reveals a complex array of data sources that collectively provide a comprehensive evidence base for the safety of the medicinal product.

Each source of adverse reaction data has its advantages and disadvantages concerning the quality of the evidence it provides, emphasising the importance of all data sources in enhancing the knowledge about pharmaceutical safety. Spontaneous reports related to authorised medicinal products generate a substantial volume of data. However, the lack of background frequencies is a significant disadvantage compared to controlled clinical trials, where frequency comparison is possible. While registry studies allow for such comparisons, they lack the medical causality assessment that are conducted for each recorded adverse event in a clinical trial (Figure 4).

Where the array of data sources is complex when it comes to authorised medicinal products, the sole source of evidence is clinical trials when it comes to non-authorised medicinal products. In this case, the safety profile has not been validated by means of a marketing authorisation application, and no post-marketing monitoring has begun. Hence, thorough adverse event management is essential, above all to safeguard the safety of patients and, secondly, to ensure a fit-for-purpose evidence for any future marketing authorisation application.

Exposure will be lowest in the development phase and will in most instances increase significantly once the product receives marketing authorisation. In the first two years following market placement in the EU, the medicinal product is subject to additional monitoring. The additional monitoring may be extended, reflecting the need for further evidence, and hence is important to consider when evaluating the product's exposure and evidence base for setting the necessary risk level of adverse event management.

Figure 4 Evidence base for safety data



7. Change log

Changes from version 1.0 to 2.0:

Version 2.0 includes the following updates:	• Section 2.2: New wording concerning additional monitoring list in the EU. • Section 2.4: Clarification and new wording concerning trials with high mortality and establishing DSMB. • Section 2.5: Clarification of which events must be included in ASR. • Editorial changes throughout the document, including changes to the layout.